A STUDY ON INFLAMMATORY MARKERS LEVEL IN ELDERLY WITH COMORBID ILLNESS, WITHOUT COMORBID ILLNESS AND WITH FRAILTY ATTENDING GOVERNMENT GENERAL HOSPITAL, CHENNAI- A CLINICAL AND BIOCHEMICAL PROFILE.

Dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI

In partial fulfillment of the
requirement for the degree of

M.D. BRANCH XVI

GERIATRICS

MADRAS MEDICAL COLLEGE

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2011

DECLARATION

I hereby declare that this dissertation entitled **"A Study on Inflammatory markers level in elderly with Comorbid illness, without Comorbid illness and with Frailty attending Government General Hospital, Chennai- A Clinical and Biochemical profile"** has been prepared by me under the guidance of Dr. B. Krishnaswamy M.D., Professor and HOD, Department of Geriatrics, Madras Medical College, Chennai in partial fulfillment of the regulations for the award of the degree of M.D. Branch XVI (Geriatrics), examination to be held in April 2011.

This study was conducted at Madras Medical College and Government General Hospital, Chennai.

I have not submitted this dissertation previously to any university for the award of any degree or diploma.

Place: Chennai Signature of candidate

Date: Name: Dr.S.SABITHA

ACKNOWLEDGEMENT

I gratefully acknowledge and sincerely thank **Dr. J.MOHANASUNDARAM M.D. Ph.d,** Dean, Madras Medical College for granting me permission to carry out this study.

I would like to express my sincere thanks and profound gratitude to my Professor and Guide **Dr. B.KRISHNASWAMY M.D.,** professor And HOD, Department of Geriatrics, Madras Medical college for his valuable guidance.

I am grateful to **Dr. S. GEETHA LAKSHMI M.D.** Professor and HOD, **Dr. G.JAYALAKSHMI M.D.,** associate professor, Department of Microbiology, Madras Medical College for her valuable guidance in carrying out this study.

I am indebted to **Dr.S.SIVAKUMAR M.D.,** Reader in Department of Geriatrics extending his moral support and valuable suggestions for this study.

I am indebted to **Dr.G.Usha M.D.,** Assistant professor of Geriatric Medicine, Madras Medical College for her help in planning the study and for her expert guidance.

I am extremely thankful to all the lab technicians Mr.Thirumoorthi, Mr.R.Ramesh, Mr.R.Narayanan in Department of Microbiology for having done all the biochemical investigation.

My sincere thanks and gratitude to all the patients in reverence to the extreme cooperation they rendered throughout the study and I wish them all good health.

CERTIFICATE

This is to certify that the dissertation entitled **"A Study on Inflammatory markers level in elderly with Comorbid illness, without Comorbid illness and with Frailty attending Government General Hospital, Chennai- A Clinical and Biochemical profile"** is a bonafide work done by Dr.S.Sabitha at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for the award of M.D., Degree in Geriatrics (Branch XVI) under my guidance and supervision during the academic year 2008-2011.

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INTRODUCTION

Chronic inflammation has been implicated as predictor and contributor of aging and age associated diseases. Inflammation involves elevation of serum inflammatory markers such as C-Reactive protein, interleukin-6.

Association of cardiovascular diseases and elevated level of inflammatory markers is well known. Many studies have demonstrated the association of elevated level of inflammatory markers in cardiovascular diseases. Absence of vascular disease has been established as a major determinant of longevity.

Recent studies have shown elevated level of serum inflammatory markers such as Interleukin-6, C-reactive protein in diseases primarily associated with aging like Coronary heart disease, diabetes mellitus, systemic hypertension, stroke, Dementia, Frailty, Osteoarthritis, Osteoporosis, Cancer, Rheumatoid Arthritis.

Frailty is a syndrome of age associated decline in physiological reserve , and has been associated with chronic inflammation. Recent

studies have shown elevated level of serum inflammatory markers in frailty and adverse health outcome.

Serum inflammatory markers may well evolve in to a more usefull clinical tool that can help to identify the most vulnerable elders and guide preventive intervention.

In this study, the association of inflammatory marker in the sub groups namely healthy elders, frail elders and elders with comorbid illness will be analysed.

AIM OF THE STUDY

1. To Compare the level of inflammatory markers Interleukin-6, High-sensitivity C-Reactive protein in elderly patients

    i) Healthy elders (without comorbid elders)

    ii) Frail elders

    iii) With comorbid illness

2. To correlate the role of Infammatory markers in Aging.

3. To analyse whether elevated level of inflammatory markers could be used in predicting the risk of aging in elders, with a view of primary prevention.

MATERIALS AND METHODS

Setting

Outpatient and Inpatient setting of the Department of Geriatric Medicine, Madras Medical College & Government General Hospital, Chennai.

Study Design

Single Center, Cross Sectional, clinical and analytical study

Period of study

August 2008 to September 2010.

Sample size

90

Selection of patients

Inclusion criteria

90 elderly patients age more than 75years from Geriatric outpatient and inpatient Department are included in the study.

Exclusion criteria

1. Acutely toxic patients

2. Rheumatoid arthiritis, chronic liver disease, Multiple myeloma, Proliferative diseases like psoriasis, mesangial proliferative glomerulonephritis.

Analysis

Data analysed using statistical package SPSS software

Details of the study

90 patients age more than 75years from Geriatic outpatient and Inpatient Department were enrolled.

The study subjects enrolled in three following sub groups:

i) 30 patients without comorbid elders (Healthy elders)

ii) 30 Frail elders according to Fried's criteria

iii) 30 patients with comorbid illness (DM, SHT, CHD, CVA, Dementia)

All the study subjects were interview during their first visit and medical history obtained. This included their name, age, sex, OP/IP no., presenting complaints. History of comorbid illness and duration of

illness (DM, SHT, CHD, CVA, Dementia) and medication used. History of substance abuse like tobacco smoking and alcohol, duration of abuse.

The patients were explained of the methods and objectives of the study and an informed consent was obtained. A detailed general examination was carried out that included pulse rate, blood pressure. Systemic examination was done.

In all patients Mini Mental Score Examination was done. Patients having score less than 24 is considered as having dementia. Patients educational status was enrolled.

Patients with frailty are categorized according to “FRIED’S criteria of frailty” which includes:

1.Gait speed

2.Hand grip strength

3.Weight loss

4.Physical activity

5.Self reported physical exhaustion

Score: 0 = No frailty

1 &2 = Prefrail

3 and above = frailty

The following investigation were done in all sub groups ESR, hemoglobin, blood sugar, serum urea and creatinine, lipid profile, Interleukin 6 level was measured by ELISA method and High-sensitivity C- Reactive protein by Immunoturbidimetry method, 12 lead ECG, CXR-PA, CT Brain if available are documented.

High-sensitivity C- Reactive protein by Immunoturbidimetry method.

Mode of reaction	Fixed time
Slope of reaction	Increasing
Wavelength	546nm
Temperature	37º C
Calibrator concentration	63 mg/L
Delay time	5 sec
Time interval	120 sec
Sample volume	2.5µl
Reagent volume	500µl
Cuvette path length	1cm light path
Method	Immunoturbidimetry method.
Normal range	Serum up to 6.0mg/L

Human IL-6 ELISA method

Preparation of standard = 200 pg/ml

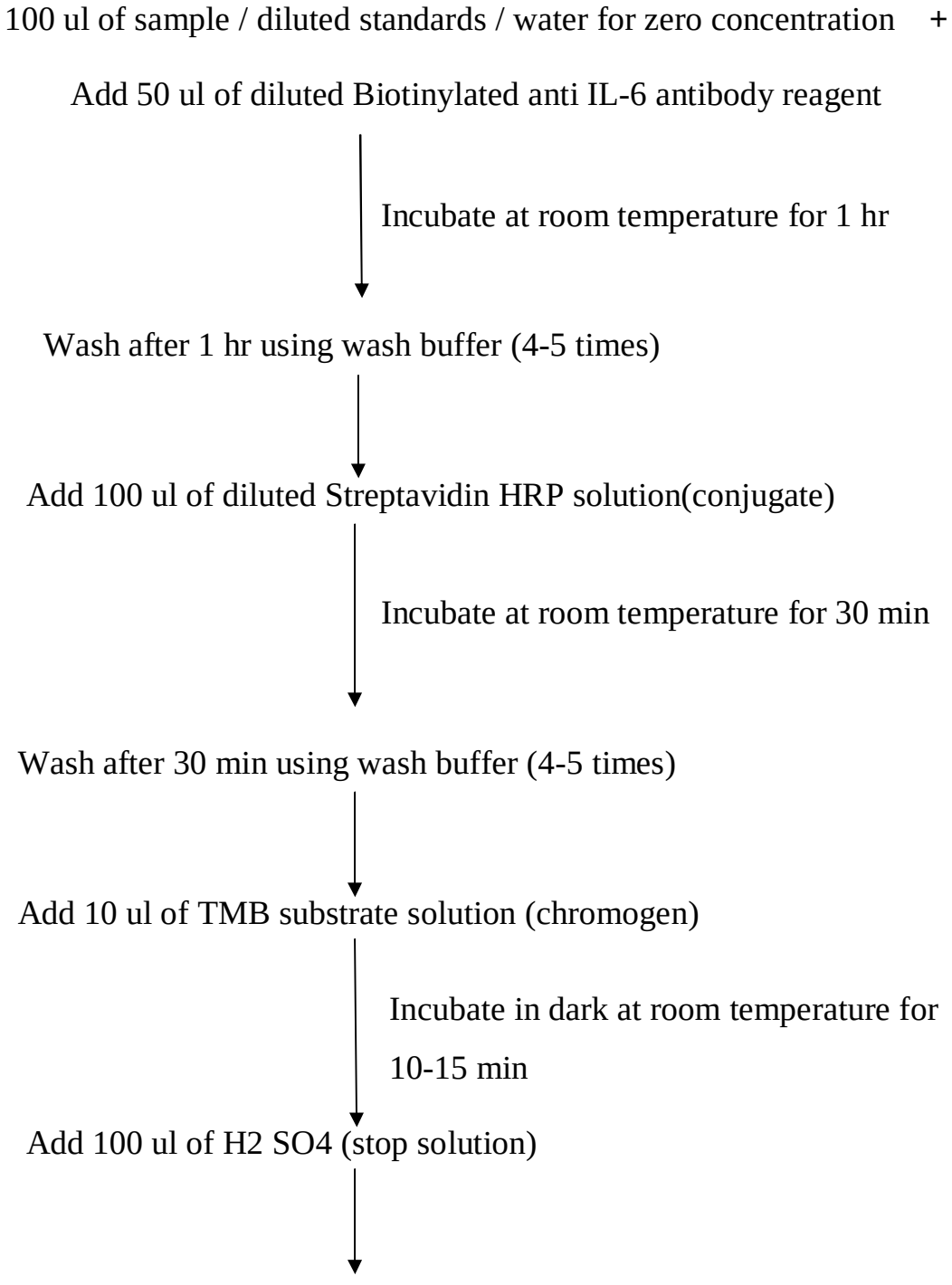
Serial dilution for the stock standard = (using standard diluents buffer)

Stock standard	200 pg/ml	1 in 1 dilution = 100 pg/ml
	100 pg/ml	1 in 1 dilution = 50 pg/ml
	50 pg/ml	1 in 1 dilution = 25 pg/ml
	25 pg/ml	1 in 1 dilution = 12.5 pg/ml
	12.5 pg/ml	1 in 1 dilution = 6.25 pg/ml

Note:

1 in 1 dilution means take equal parts of standard and standard diluents buffer.

Test Protocol for Human IL-6



REVIEW OF LITERATURE

INFLAMMATION AND AGEING

Ageing is accompanied by 2-4 fold increases in serum levels of inflammatory mediators, such as cytokines and acute-phase proteins[1].

The term "Inflammaging" has been coined by Claudio Franceschi to explain the now widely accepted phenomenon that ageing is accompanied by a low-grade chronic, systemic up-regulation of the inflammatory response and that the underlining inflammatory changes are also common to most age-associated diseases[2-9].

Inflammation has been classically characterized by the cardinal signs of heat, pain, swelling and redness. But inflammation also operates at a much lower level. This marks a shift from the old view of inflammation (either present or absent) to the new (always “present” but to varying degrees)[10].

Acute inflammation is well known to be associated with the five cardinal features 1. rubor (redness), 2. tumor (swelling), 3. dolor (pain), 4. calor (warm), 5. functio lesa (loss of function). on the contrary, inflammaging is characterized by the complex set of five features which

can be described as 1. low-grade, 2. controlled, 3. asymptomatic, 4. chronic, 5. systemic, inflammatory state.

In most superifical process, inflammation is localized and does not usually result in a measurable systemic reponse. However in major infection or injuries, systemic activation of inflammatory pathways result in measurable elevations in circulating inflammatory cytokines and other acute phase reactant proteins[11.]

Inflammation involves systemic markers often liver proteins such as CRP and fibrinogen, paracrine / endocrine local markers such as IL- 6 and TNFα, and cell-cell interaction markers such as E-selectin and intercellular adhesion molecule-1.

Inflammation involves a cascade in which tissue injury stimulates cells to make pro-inflammatory cytokines, which in turn stimulate hepatocytes to produce acute phase proteins and inflammatory markers.

Aging has also been associated with increased levels of circulating inflammatory components in the blood including elevated concentrations of TNF-alpha, IL-6, acute-phase proteins such as C-reactive protein and serum amyloid A, and high neutrophil counts.

This increase, however, in circulating inflammatory parameters in healthy elderly humans is small and far less than levels seen during acute infections.

A wide range of factors seems to contribute to this low-grade inflammation, including an increased amount of fat tissue, decreased production of sex steroids, smoking, subclinical infections such as Chlamydia pneumonia, Helicobacter pylori, dental infections and asymptomatic bacteriuria may play a role and such chronic disorders as cardiovascular diseases and Alzheimer's disease.

Aging itself is associated with complex changes in the immune system. There is a progressive increase in the concentration of glucocorticoids and catecholamines with aging, and decreased production of growth and sex hormones, a pattern suggestive of that seen in chronic stress.

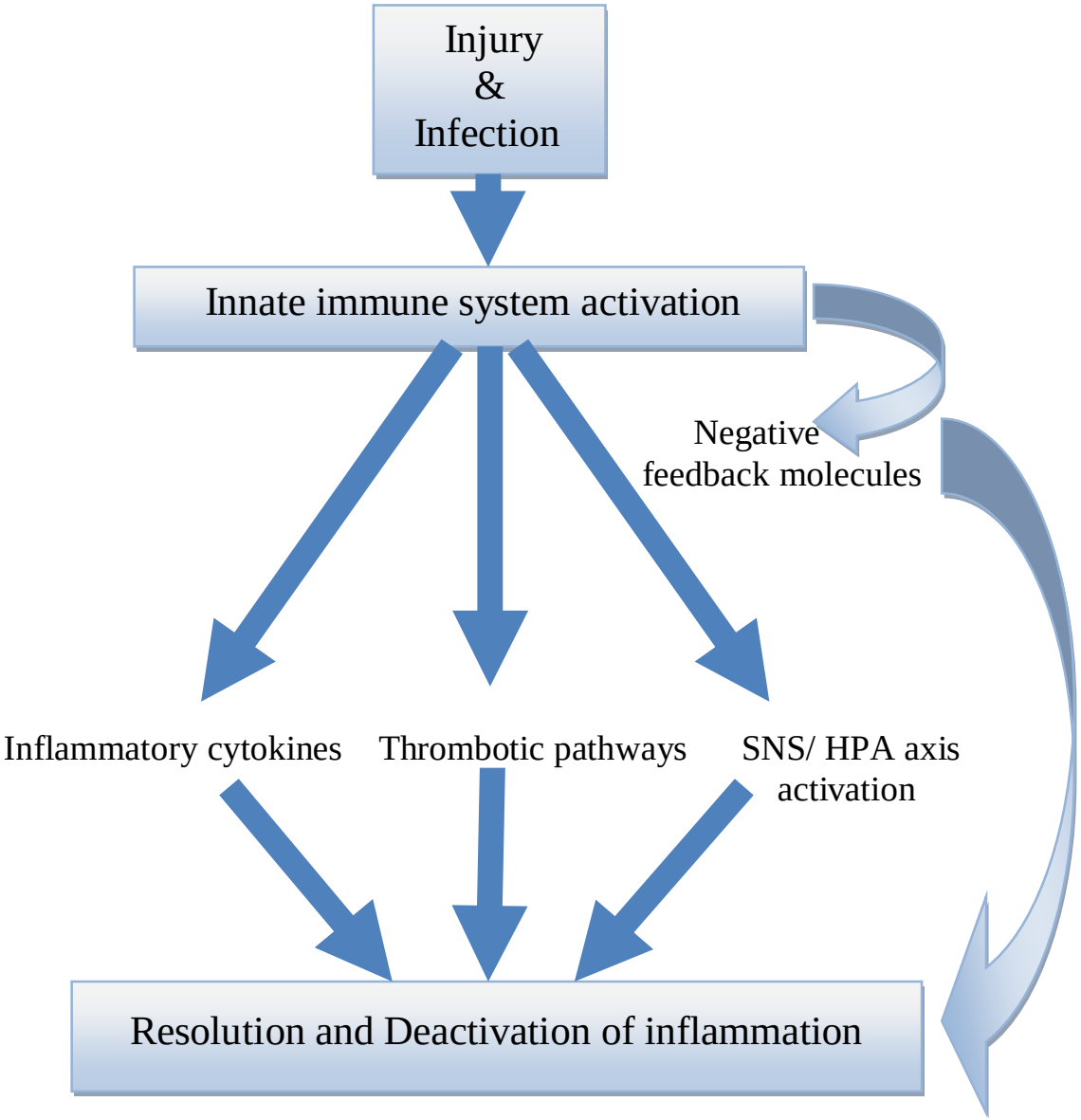
The inflammatory scenario that characterizes inflammaging constitutes a highly complex response to various subtle internal and environmental inflammatory stimuli mediated mainly by the increased circulating levels of pro inflammatory cytokines. Inflammaging also generates Reactive Oxygen Species (ROS) causing both oxidative

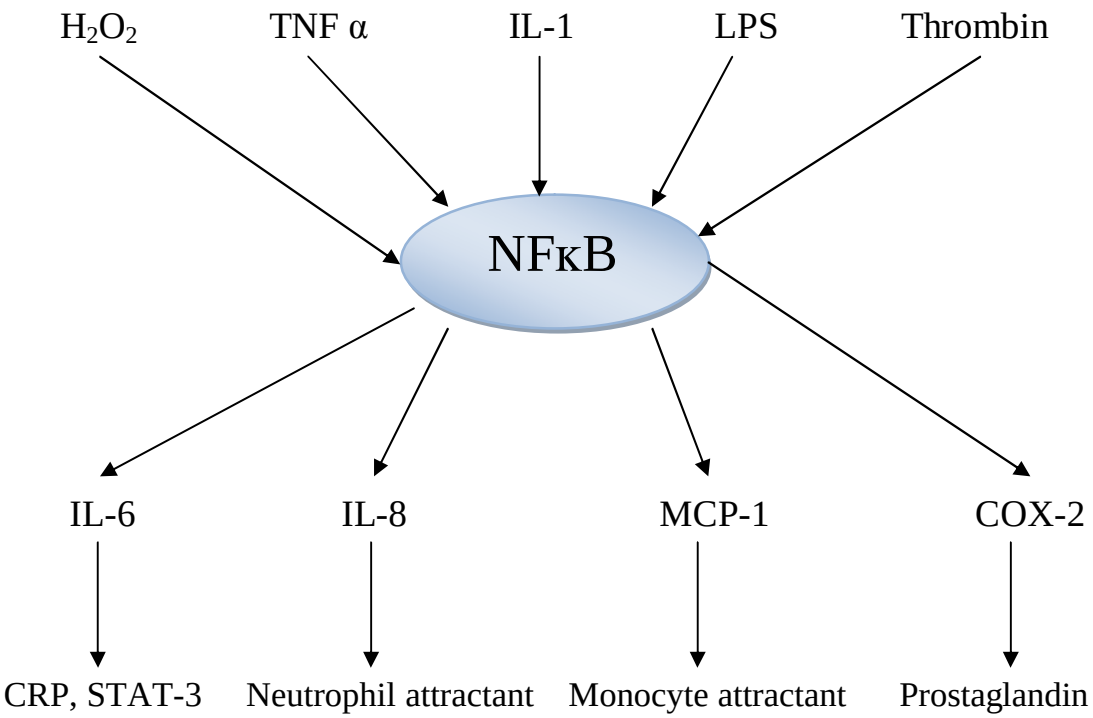
damage and eliciting an amplification of the cytokines release, thus perpetuating a vicious cycle resulting in a chronic systemic pro inflammatory state where tissue injury and healing mechanisms proceed simultaneously and damage slowly accumulates asymptomatically over decades and is a major determinant both of the ageing process and of the development of age-associated diseases .

Inflammaging is triggered by the first line of biological defense i.e. the innate immunity that operates by detection of a broad range of injuries inducing the activation of inflammatory responses. The mononuclear phagocytes lineage plays a pivotal role in innate immunity that does not require clonal expansion of cell populations . Moreover, several other cell types contribute to innate immunity by expressing pattern recognition receptors, namely various scavenger and Toll like receptors . These cell encoded proteins recognize ligands from damaged tissues and induce host responses by transmembrane signals that activate NFkB and mitogen dependent protein kinase pathway . Toll like receptor activation also induces the expression of a wide variety of number of genes encoding proteins, such as cytokines, with regulatory functions upon cell activations and tissue inflammation .

Inflammaging as a summary of the physiological and molecular changes consistent with the aging process that are known to be associated with chronic activation of inflammatory pathways[11].

Normal inflammatory response to injury or infection. With activation of multiple physiological pathways and ultimately resolution of response.





Schematic of the inflammatory gateway nuclear transcription factor NFκB, along with inflammatory triggers (row A), and inflammatory outflow (rows B and C). Row A shows specific inflammatory stimuli that lead to NFκB activation via specific cell receptors and specific signal transduction pathways (not shown). Activated subunits of NFκB in turn leads to the expression of proteins that provide negative feedback for inflammation (not shown) or that propagate inflammatory message (row B) and influence the activation of other pathways (row C) that influence inflammatory response, thrombosis and the expression of other proteins.

Aging is associated with a dysregulated cytokine response following stimulation. Cytokines are potent anorectic agents. Many older persons have mild inflammatory disorders that lead to anorexia[12]. cytokines play a role in the pathogenesis of anorexia and sarcopenia, thus accelerating the development of frailty in older persons[13].

Increased cerebral secretion of cytokines due to a wide range of physically stressful events plays an important role in the occurrence of delirium[14].

Increased IL-6 levels leads to loss of muscle and bone mass, fever, activation of the hypothalamic-pituitary-adrenal axis, activation of the hepatic acute-phase response, and hemodilution resulting in a decline in hemoglobin levels[15-18].

In bone, IL-6 is produced by osteoblasts and promotes osteoclast activity and subsequent bone resorption[19]. Numerous acquired influences such as visceral obesity, smoking, stress also trigger IL-6 release.

IL-6 and CRP associated with adverse health outcomes and disease states in older adults[11]. In older persons, CRP has been shown to be a marker of functional decline and mortality[20-23]

Cigarette smoking has been shown to promote higher levels of IL-6. Exercise may be an efficacious therapy for restoring immune function in the elderly. Long-term exercise interventions appear to be promising.

Serum inflammatory markers may well evolve into a more useful clinical tool that can help identify the most vulnerable older adults and guide therapeutic or preventive interventions[11.]

The basic steps to reduce inflammation in the body include:

- Better dental hygiene - Low grade gum infections are extremely common and have a major negative impact on heart disease.

- Exercise - Evidence indicates that regular exercise improves low grade chronic inflammation. It may worsen acute or active chronic inflammation.

- Weight loss - Obesity appears to increase the overall level of inflammation in the body.

- No smoking - Smoking floods the systems with free radicals and irritants, promoting inflammation and other forms of damage.

- Anti-inflammatory diet - Diet has an impact on the overall level of inflammation in body. A number of dietary adjustments can help minimize inflammation, including the following: reducing or eliminating saturated and trans fat; increasing the intake of omega-3 fat (fish, fish oil, flaxseed oil); increasing consumption of fruits and vegetables. Anti-inflammatory diet should be high in fiber and favor low glycemic foods. Research indicates that animal protein may be somewhat proinflammatory. To reduce inflammation, use protein from non-animal sources like fish, soy, beans and nuts.

- Drugs

  COX- inhibitors e.g. aspirin

  Statins e.g. lipitor

  Proteases e.g. serrapepditase, nattokinase, bromelain

  LOX-inhibitors e.g. acetyl-boswellic acid.

C-reactive protein (CRP)

CRP is a protein found in the blood, the levels of which rise in response to inflammation an acute-phase protein. Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the C1Q complex[24].

CRP is synthesized by the liver[25] in response to factors released by fat cells (adipocytes).[26] It is a member of the pentraxin family of proteins.[25] It is not related to C-peptide or protein C.

History and nomenclature

CRP was originally discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with the *C* polysaccharide of pneumococcus.[27] Initially it was thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer,[25] however discovery of hepatic synthesis demonstrated that it is a native protein.

Function

CRP is a member of the class of acute-phase reactants, as its levels rise dramatically during inflammatory processes. This increment is due to a rise in the plasma concentration of IL-6, which is produced predominantly by macrophages[25] as well as adipocytes. CRP binds to phosphocholine on microbes. It is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages, which express a receptor for CRP.

CRP rises up to 50,000-fold in acute inflammation, such as infection. It rises above normal limits within 6 hours, and peaks at 48 hours. Its half-life is constant, and therefore its level is mainly determined by the rate of production and hence the severity of the precipitating cause. Serum amyloid A is a related acute-phase marker that responds rapidly in similar circumstances.[25]

Diagnostic use

CRP is used mainly as a marker of inflammation. Apart from liver failure, there are few known factors that interfere with CRP production.[25]

Measuring CRP values can prove useful in determining disease progress or the effectiveness of treatments. Blood, usually collected in a serum-separating tube, is analysed in a medical laboratory. Various methods are available for CRP determination, such as ELISA, immunoturbidimetry, rapid immunodiffusion, and visual agglutination.

When to start testing CRP

Elevated C-Reactive Protein levels provide information on cardiovascular risk over the age of 30-40 years. Can detect risk years in advance and have the opportunity to initiate lifestyle and pharmacologic interventions in order to prevent heart attack or stroke.

High-sensitivity CRP test (**hs-CRP**)

hsCRP measures low levels of CRP using laser nephelometry. The test gives results in 25 minutes with a sensitivity down to 0.04 mg/L. Normal concentration in healthy human serum is usually lower than 10 mg/L, slightly increasing with ageing. Higher levels are found in late pregnant women, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), severe bacterial infections and burns (>200 mg/L)[28]

Difference between regular CRP and hs-CRP tests

Both tests measure the same molecule in the blood. The hs-CRP test is to determine the risk of cardiovascular disease. It measures CRP in the range from 0.5 to 10 mg/L. The CRP is done in patients at risk for bacterial or viral infection, patients with chronic inflammatory diseases (such as rheumatoid arthritis). It measures CRP in the range from 10 to 1000 mg/L.

Conditions that lower CRP levels

Lliver disease, weight loss, exercise, moderate alcohol intake, and lipid lowering agents that inhibit hepatic hydroxyl methyl glutaryl coenzyme A.

Cardiology diagnostic test

Arterial damage results from white blood cell invasion and inflammation within the wall. CRP is a general marker for inflammation and infection, so it can be used as a very rough proxy for heart disease risk. Since many things can cause elevated CRP, this is not a very specific prognostic indicator.[29]

Role in cardiovascular disease

AHA/CDC risk assessment guidelines[30] (American Heart Association and Centers for Disease Control & Prevention)

Low risk	<1 mg/L
Average risk	1-3 mg/L
High risk	>3 mg/L

In the capture trail, CRP levels of >10mg/L doubled the event rate (mortality or MI), compared to CRP levels of <10mg/L.

Recent research suggests that patients with elevated basal levels of CRP are at an increased risk of diabetes,[31,32] hypertension and cardiovascular disease.

Treatment to lower CRP

Lowering C-Reactive Protein will result in a direct lowering of cardiovascular risk. CRP is lowered by diet, exercise, blood pressure control and quiting smoking.

The JUPITER trial was conducted to determine if patients with elevated CRP levels but without hyperlipidemia might benefit from statin therapy. Statins were selected because they have been proven to reduce levels of CRP[2] . The trial found that patients taking rosuvastatin with elevated CRP levels experienced a decrease in the incidence of major cardiovascular events[33]. The trial specifically found, after four years of treatment, out of every 31 patients, one cardiovascular event would be prevented.

Interleukin-6

Interleukin-6 is a protein that in humans is encoded by the *IL6* gene. [34] IL-6 is an interleukin that acts as both a pro inflammatory and anti inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response to trauma, especially burns or other tissue damage leading to inflammation. In terms of host response to a foreign pathogen, IL-6 has been shown in mice, to be required for resistance against the bacterium, *Streptococcus pneumoniae*.[35]

IL-6 is also a "myokine," a cytokine produced from muscle, and is elevated in response to muscle contraction.[36] It is significantly elevated with exercise, and precedes the appearance of other cytokines

in the circulation. During exercise, it is thought to act in a hormone-like manner to mobilize extracellular substrates and augment substrate delivery (Petersen, J Appl Physiology 2005).

Osteoblasts secrete IL-6 to stimulate osteoclast formation. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine. IL-6's role as an anti-inflammatory cytokine is mediated through its inhibitory effects on TNF-alpha and IL-1, and activation of IL-1ra and IL-10.

A cytokine for gerontologists[37].

Interleukin-6 is a proinflammatory cytokine that is normally tightly regulated and expressed at low levels, except during infection, trauma, or other stress[38,39].

Among several factors that down-regulate IL-6 gene expression are estrogen and testosterone. After menopause or andropause, IL-6 levels are elevated, even in the absence of infection, trauma, or stress.

IL-6 is a potent mediator of inflammatory processes, and it has been proposed that the age associated increase in IL-6 accounts for the phenotypic changes of advanced age, particularly those that resemble

chronic inflammatory disease (decreased lean body mass, osteopenia, low grade anemia, decreased serum albumin and cholesterol, and increased inflammatory proteins such as C-reactive protein and serum amyloid A).

The age-associated rise in IL-6 has been linked to lymphoproliferative disorders, multiple myeloma, osteoporosis, and Alzheimer's disease. Higher circulating levels of IL-6 predict disability onset in older persons. This may be attributable to a direct effect of IL-6 on muscle atrophy and to the pathophysiologic role played by IL-6 in specific diseases.[40.]

Function

IL-6 is one of the most important mediators of fever and of the acute phase response. It is capable of crossing the blood brain barrier and initiating synthesis of PGE2 in the hypothalamus, thereby changing the body's temperature. In the muscle and fatty tissue IL-6 stimulates energy mobilization which leads to increased body temperature.

IL-6 can be secreted by macrophages in response to specific microbial molecules, referred to as pathogen associated molecular patterns (PAMPs). These PAMPs bind to highly important group of

detection molecules of the innate immune system, called pattern recognition receptors (PRRs), including Toll like receptors (TLRs). These are present on the cell surface and intracellular compartments and induce intracellular signaling cascades that give rise to inflammatory cytokine production.

Inhibitors of IL-6 (including estrogen) are used to treat postmenopausal osteoporosis. IL-6 is also produced by adipocytes and is thought to be a reason why obese individuals have higher endogeneous levels of CRP.

Role in disease

IL-6 is elevated in many disease processes such as diabetes, atherosclerosis, depression, Alzheimer's Disease, systemic lupus erythematosus, prostate cancer, and rheumatoid arthritis. Advanced cancer patients have higher levels of IL-6 in their blood. Hence there is an interest in developing anti-IL-6 agents as therapy against many of these diseases[41.]

Treatment

1. Tocilizumab which has been approved for rheumatoid arthritis.
2. ALD518, is in clinical trials.[42]

FRALITY

As the aging population increases rapidly worldwide, caring for frail older adults has become the mandate of modern medicine. As such, frailty has been increasingly recognized as an important geriatric syndrome[43].

The prevalence of frailty is high with ranging from 10% to 25% of persons age 65 years and olders. 30% to 45% over the age 85 years[44].

Frailty is characterized by decreased functional and physiologic reserve, increased vulnerability to stressors, as well as high risk for serious adverse health outcomes including disability, dependency, and mortality[43].

The domains of frailty include poor nutritional status, reduced muscle strength, diminished lower-extremity performance, low physical activity and a sense of exhaustion[45].

Frail older adults demonstrate dysregulations in multiple physiologic systems[43]. Low grade, chronic systemic inflammation manifested in older adults, so-called “inflamm-aging,” is an important feature of immunosenescence[43].

Activation of the inflammation system marked by elevated levels of inflammatory markers, above and beyond age-related increases, is considered the most prominent pathophysiological feature of frailty[1]. Sarcopenia or loss of muscle mass with aging is central manifestation of frailty. Associated with decline in lean body mass[44].

Elevated CRP and IL-6 are associated with increased mortality in elderly. IL-6 has been associated with high risk of mobility disability[45].

Sarcopenia

A central factor in the pathophysiology of frailty Sarcopenia is the age-related loss of muscle mass [46]. It is derived from the Greek ‘‘sarx’’ for flesh and ‘‘penia’’ for loss. It has become conventional to consider an older person to be sarcopenic when the lean body mass is less than two standard deviations of the sex-specific mean in a young healthy sample. This is defined using the formula derived from measurements using dual-energy x-ray absorptiometry: Appendicular skeletal mass/height^2.

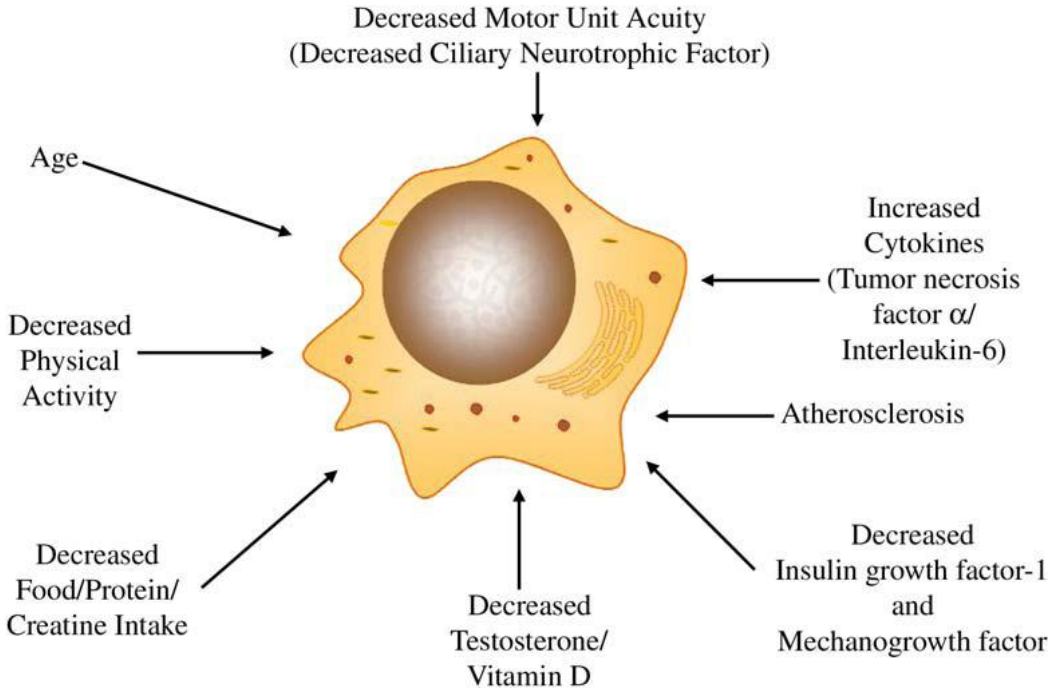
These measurements fails to take into account the quality of muscle and with aging there can be a marked uncoupling of muscle cross-sectional

area and muscle fiber strength. Also, there has been increased awareness recently that with aging there is fat accumulation in muscle (myosteatosis), which results in a decline in muscle function.

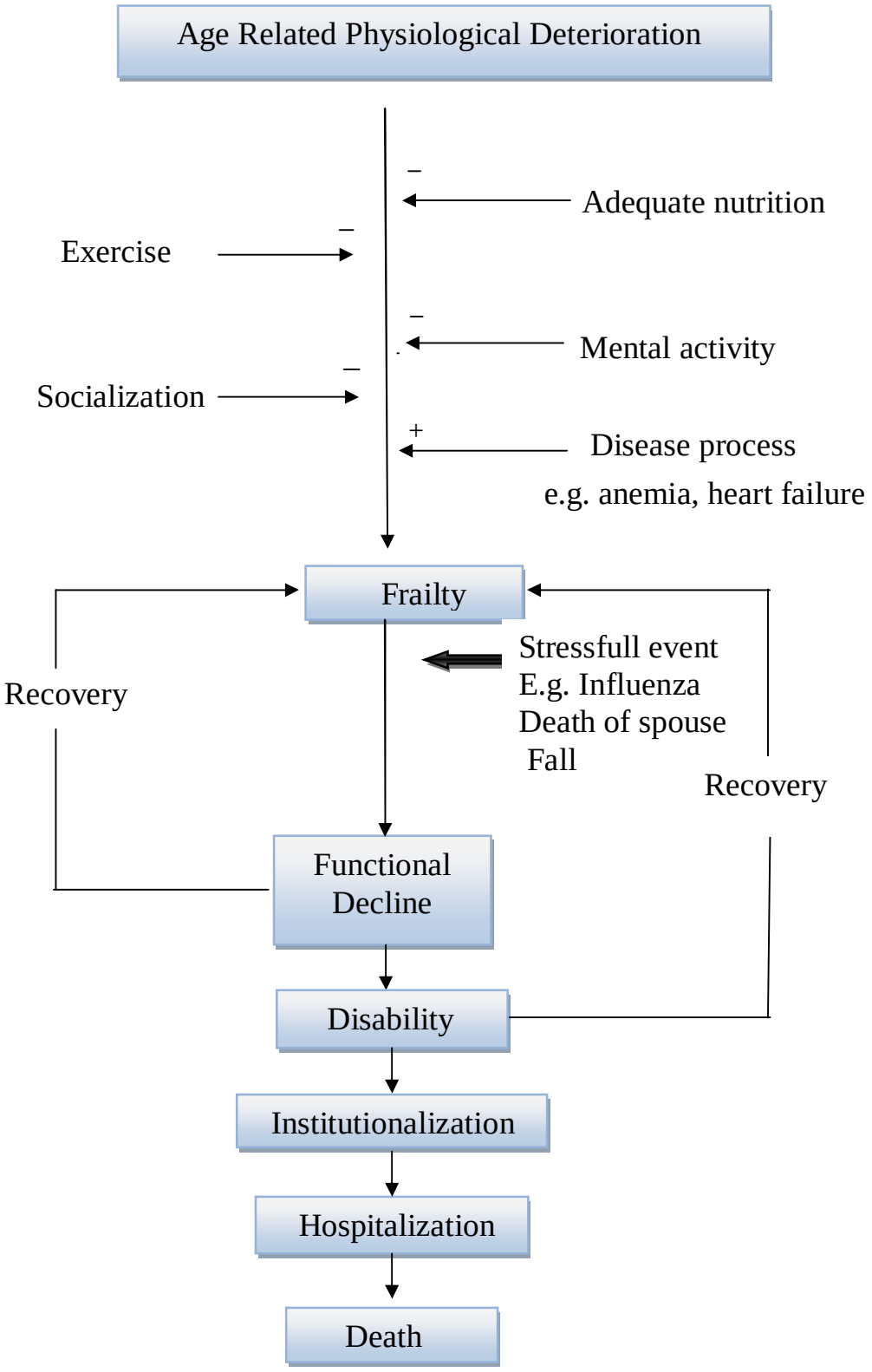
Using this definition, the prevalence of sarcopenia is approximately 12% for adults 60 to 70 years of age rising to 30% by 80 years of age.

In most studies, the development of sarcopenia is associated strongly with increased disability, gait and balance disorders and mortality [47,48]. Muscle strength also declines with aging [49].

The causes of sarcopenia.



The frailty cascade



FRIED'S crieteria for frailty[50]

1. Gait speed

If a person takes >6 to 7seconds to walk a distance of 15 feet, it is considered as slow gait speed.

2. Hand grip strength

Hand grip is measured by hand dynamometer. The participant is asked to stand up and hold the dynamometer in the dominant hand with the arm parallel to the body without sqeezing the arm against the body. Three reading was taken, best score is used. Hand grip strength was expressed in kilogrammes (kg). Score <30 in male and <18 in female is considered as having low hand grip strength.

3. Weight loss

Weight loss of >5% of total body weight in last one year.

4. Physical activity

Low physical activity in the past three months.

5. Self reported physical exhaustion

Score:

Zero = No frailty

1 and 2 = Prefrail

3 and more than three = frailty

Importance of Hand grip strength

Poor hand grip strength predicts accelerated dependency in ADL and cognitive decline in older adults. Measuring hand grip strength can be useful to identify those old patients at risk for future decline. Hand grip strength measurement is an easy to use instrument in clinical geriatric practice[51].

Preventing Frailty

Food: maintain intake

Resistance exercises

Atherosclerosis: prevent

Isolation: avoid (i.e., go out and do things)

Limit pain

Tai Chi or other balance exercises

Yearly check for testosterone deficiency

Treating of Frailty

1. Frailty should be seen as treatable and as an important stage on the road to disability and serious illness[52].

2. The first step is treat any diseases that are causing or contributing to frailty.

3. All frail person should be screened for Depression . If they are depressed they should be treated.

4. Resistance exercise is another cornerstone of the management of frailty. resistance exercise training at least three times per week.

5. Testosterone level should be measured, if it is low, testosterone replacement therapy should be started.

6. Frail elderly people should be checked for hypothyroidism. folate, vitamin B12 and vitamin B6 supplements may be usefull.

7. Early cognitive impairment may respond to cholinesterase inhibitors.

8. Balance and flexibility exercises. Tai Chi an ancient Chinese exercise form is also an excellent set of exercises to improve balance and reduce falls.

COMORBID ILLNESS

Chronic inflammation as been implicated as predictor and contributor of aging and age associated diseases.

Association of cardiovascular diseases and elevated of inflammatory markers is well known.

Inflammatory markers are elevated in diseases primarily associated with aging like DM, SHT, CHD, CVA, Dementia, Frailty, Osteoarthritis, Osteoporosis, Rheumatoid Arthritis.

CORONARY HEART DISEASE

Inflammation is an immune response to injury. Inflammation play a role in cardiovascular disease. Studies have shown an association between high levels of markers of inflammation in the circulation with a greater risk of a cardiovascular event.

A critical inflammatory marker is C-reactive protein. This marker indicates an increased risk for destabilized atherosclerotic plaque and abnormal arterial clotting. When arterial plaque becomes destabilized, it can burst open and block the flow of blood through a coronary artery, resulting in an acute heart attack. New England Journal of Medicine

studies showed that people with high levels of C-reactive protein were almost three times as likely to die from a heart attack (Ridker et al. 1997).

In coronary heart disease hsCRP, IL-6, TNF-α, homocysteine, and fibrinogen are elevated.

Inflammation markers linked more with fatal than nonfatal cardiovascular events in elderly[53.]

Three inflammatory markers—interleukin-6 , C-reactive protein and fibrinogen—were each more strongly associated with fatal cardiovascular events than with non-fatal cardiovascular events. Of all three inflammatory markers, and in particular IL-6, were more strongly associated with a fatal heart attack or stroke than with a non-fatal heart attack or stroke.

Whether it was useful to include these markers in tools designed to distinguish between individuals with a high and a low risk of heart attacks, strokes and other cardiovascular events. whether the application of inflammatory markers may help better predict the risk of deaths from cardiovascular disease, and whether novel treatments which dampen inflammation might help prolong life.

Interleukin-6 strongest CVD risk predictor in the elderly

The inflammatory markers C-reactive protein, tumor necrosis factor-α, and interleukin-6 are independent predictors of cardiovascular events in the elderly. All three markers, especially IL-6, predicted all cardiovascular events more strongly than traditional risk factors.

"Increased IL-6 level was the strongest and most consistent risk factor for cardiovascular events" IL-6 was found to have two to fivefold increase in cardiovascular events[54].

Most studies on inflammatory markers have been done in younger people and were primarily focused on CRP. Thus IL-6 and TNF-α could serve as warning signs, because they increase early in inflammation, whereas CRP increases later in the process.

"Perhaps with these measures, we can go deeper into the evaluation of cardiovascular health of the subject, and detect disease that has not yet been diagnosed." However, assessments of IL-6 and TNF-α are more difficult and costly compared with CRP measurements.

The Life Extension Foundation long ago advised members to have an annual C-reactive protein blood test to detect systemic

inflammation that could increase the risk of heart attack, stroke, cancer and a host of age-related diseases.

In fact, on January 28, 2003, the American Heart Association and Centers for Disease Control & Prevention jointly endorsed the C-reactive protein test to screen for coronary-artery inflammation to identify those at risk for heart attack.

The American Heart Association and US Centers for Disease Control and Prevention have defined risk groups as follows:

- Low risk: less than 1.0 mg/L
- Average risk: 1.0 to 3.0 mg/L
- High risk: above 3.0 mg/L

DIABETES MELLUTUS

In recent years, it has been theorized that chronic, low-grade tissue inflammation related to obesity contributes to insulin resistance, the major cause of Type 2 diabetes.

The baseline levels of C-reactive protein and interleukin-6 were significantly higher among those who subsequently developed diabetes[55].

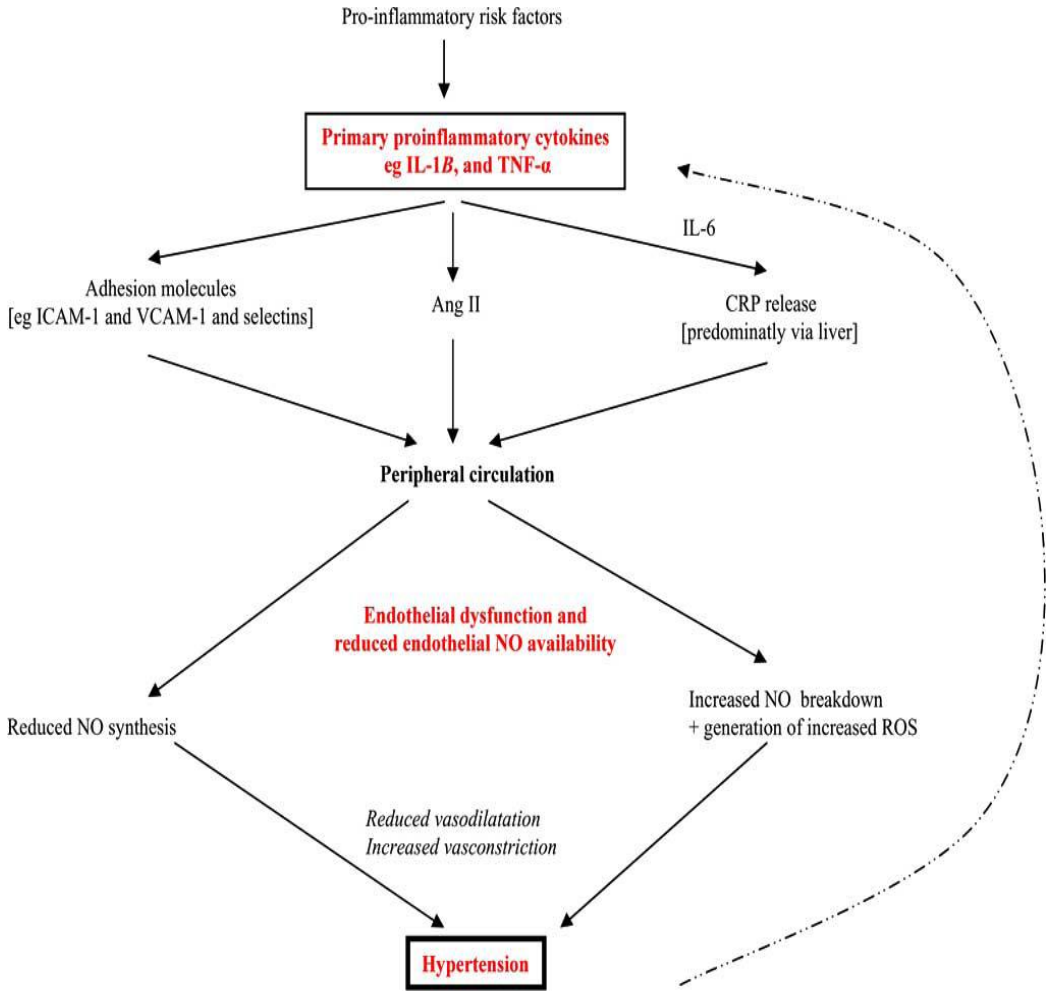
"Elevated C-reactive protein and IL-6 predict the development of Type II diabetes mellitus. These data support a possible role for inflammation in diabetogenesis."

A low-grade inflammation precedes and predicts diabetes development in adults participating in the Atherosclerosis Risk in Communities Study [56].

Several reports in various markers of inflammation in different population groups have confirmed the association of inflammation in diabetes[57-65].

Hypertension

The role of inflammation in development of hypertension



Elevated hsCRP appeared to be predictive for the development of future hypertension in apparently normotensive individuals, which might suggest that inflammation even precedes the subsequent development of hypertension [66].

CEREBRO VASCULAR ACCIDENTS

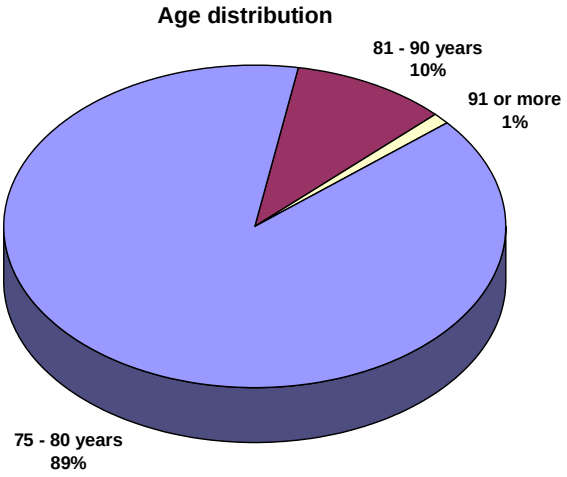
Markers of inflammation, including peak plasma CRP, WBC count, ESR or plasma cortisol, were associated with severity of stroke, CT brain infarct volume or clinical outcome[67,68].

DEMENTIA

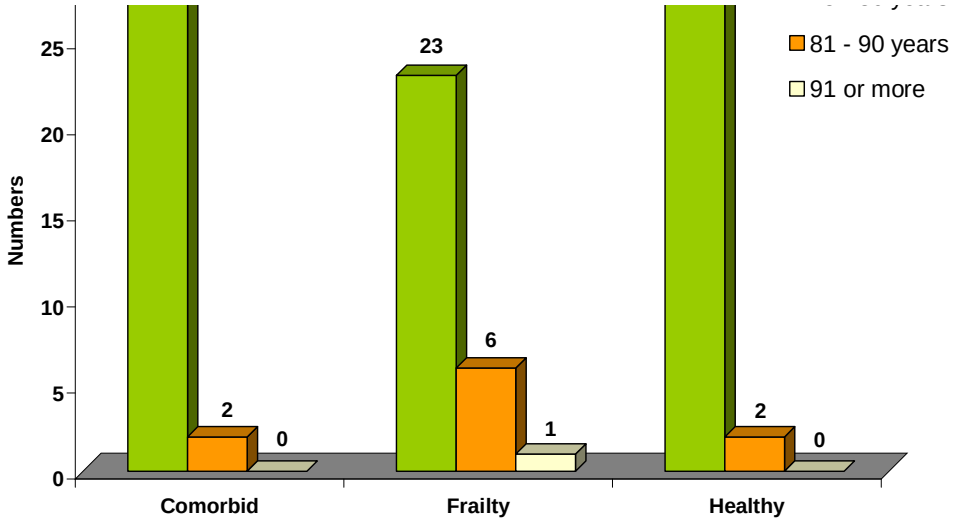
Inflammation has been involved in the pathogenesis of dementia. The study evaluates the presence and the source of pro- and anti-inflammatory cytokines in the blood of patients with Alzheimer's disease , multi-infarct dementia [69.] The combination of high CRP and high IL6 was associated with risk of Vascular dementia[70.]

OBSERVATIONS AND RESULTS

Percentage of Age distribution



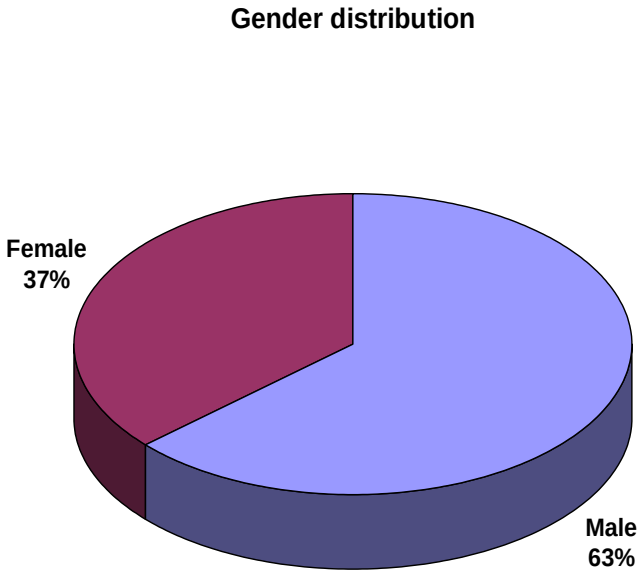
Comparison between Various groups



Age group

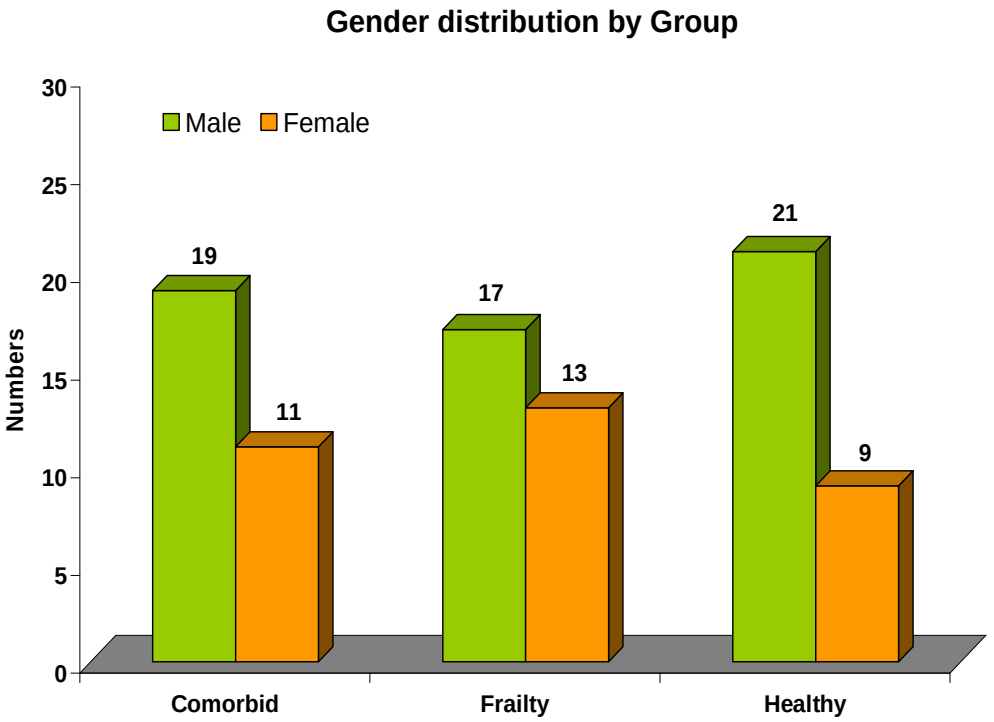
Group		Frequency	Percent
Comorbid	75 - 80 years	28	93.3
	81 - 90 years	2	6.7
	Total	30	100.0
Frailty	75 - 80 years	23	76.7
	81 - 90 years	6	20.0
	91 or more	1	3.3
	Total	30	100.0
Healthy elders	75 - 80 years	28	93.3
	81 - 90 years	2	6.7
	Total	**30**	**100.0**

Gender distribution



Gender

	Frequency	Percent
Male	57	63.3
Female	33	36.7
Total	90	100.0



Gender

Group		Frequency	Percent
Comorbid	Male	19	63.3
	Female	11	36.7
	Total	30	100.0
Frailty	Male	17	56.7
	Female	13	43.3
	Total	30	100.0
Healthy elders	Male	21	70.0
	Female	9	30.0
	Total	30	100.0

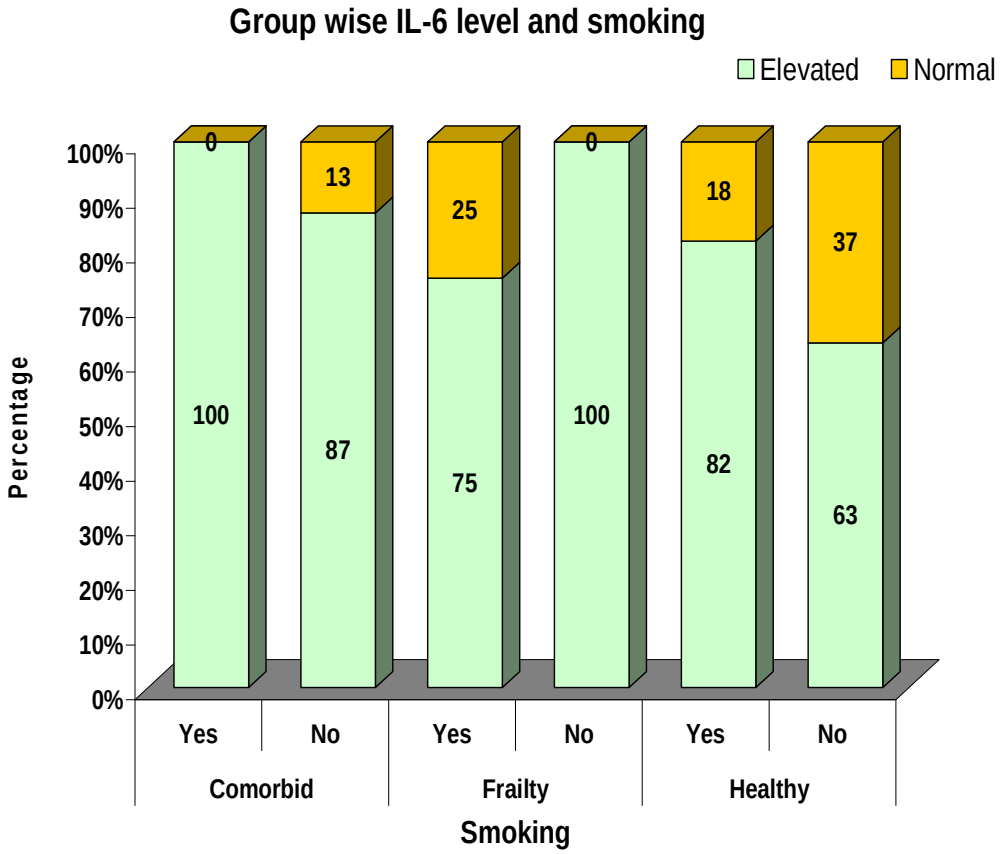
SMOKING

	Frequency	Percent
No	64	71.1
Yes	26	28.9
Total	90	100.0

Group wise Frequency Table

SMOKING

Group		Frequency	Percent
Comorbid	No	23	76.7
	Yes	7	23.3
	Total	30	100.0
Frailty	No	22	73.3
	Yes	8	26.7
	Total	30	100.0
Healthy elders	No	19	63.3
	Yes	11	36.7
	Total	30	100.0


Group wise IL-6 level and smoking
Elevated
Normal
Percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
13
25
0
18
37
100
87
75
100
82
63
Yes
No
Yes
No
Yes
No
Comorbid
Frailty
Healthy
Smoking

COMORBID ILLNESS

Diabetes Mellitus

	Frequency	Percent
No	16	53.3
Yes	14	46.7
Total	30	100.0

Systematic Hypertension

	Frequency	Percent
No	10	33.3
Yes	20	66.7
Total	30	100.0

Coronary heart disease

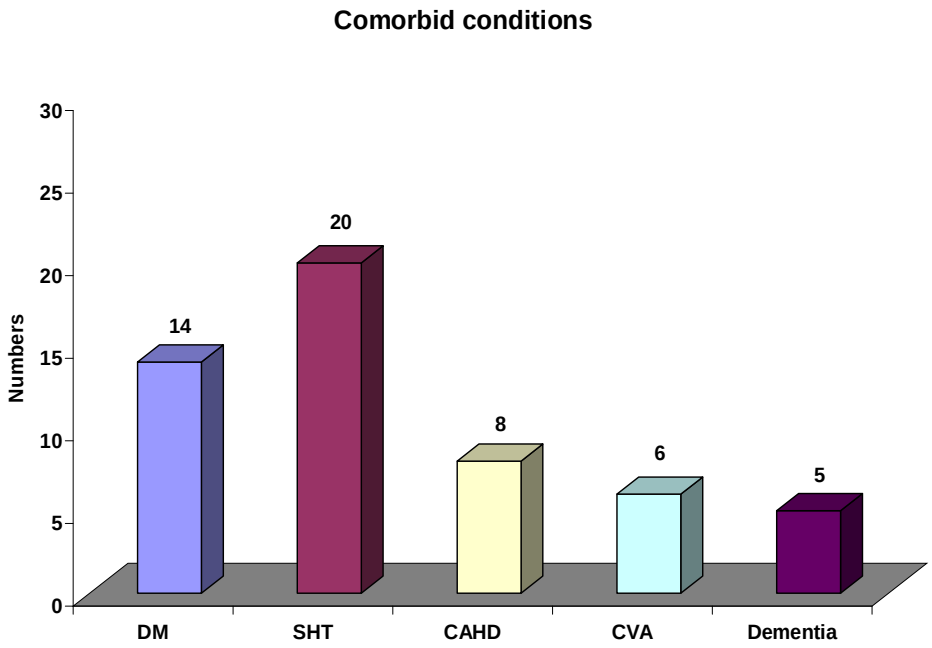
	Frequency	Percent
No	22	73.3
Yes	8	26.7
Total	30	100.0

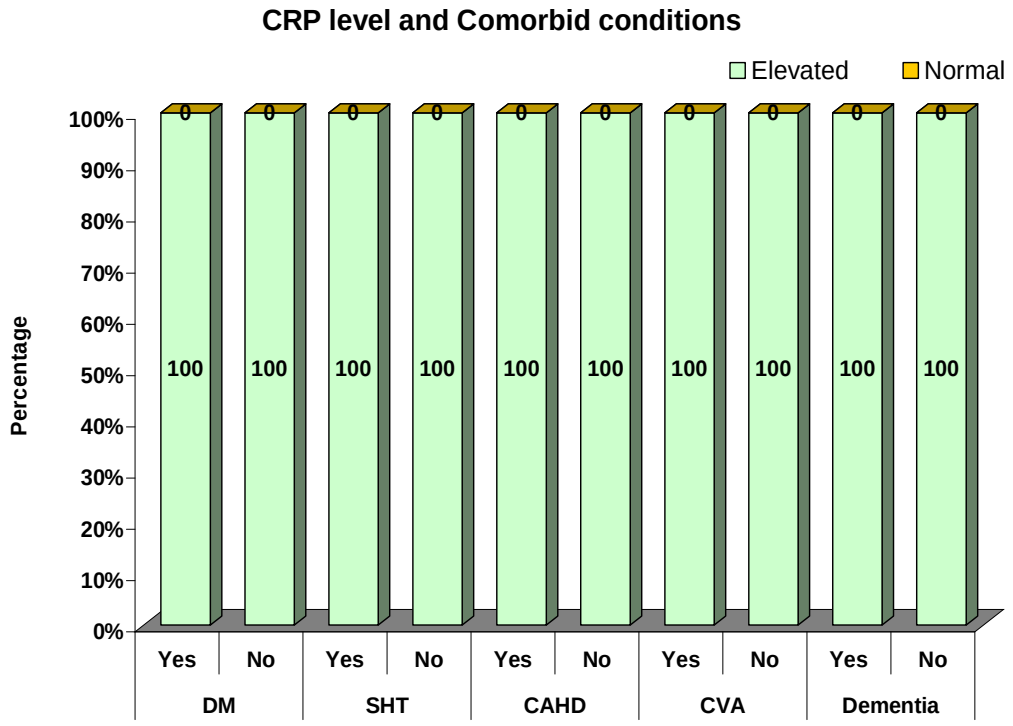
Stroke

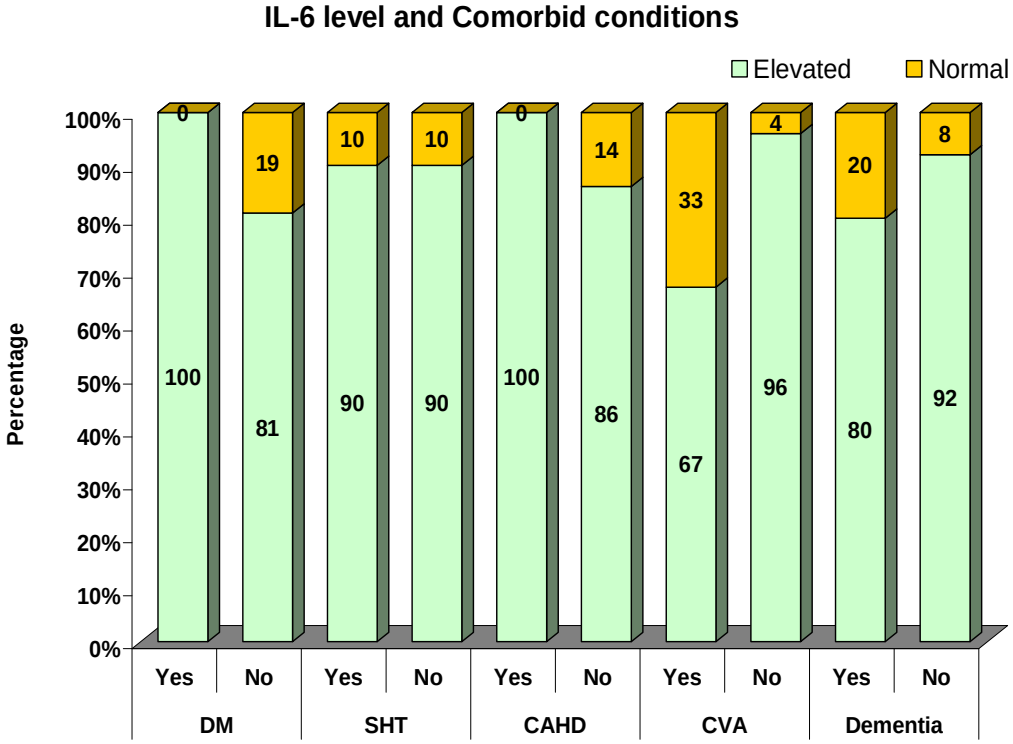
	Frequency	Percent
No	24	80.0
Yes	6	20.0
Total	30	100.0

Dementia

	Frequency	Percent
Normal	25	83.3
Dementia	5	16.7
Total	30	100.0

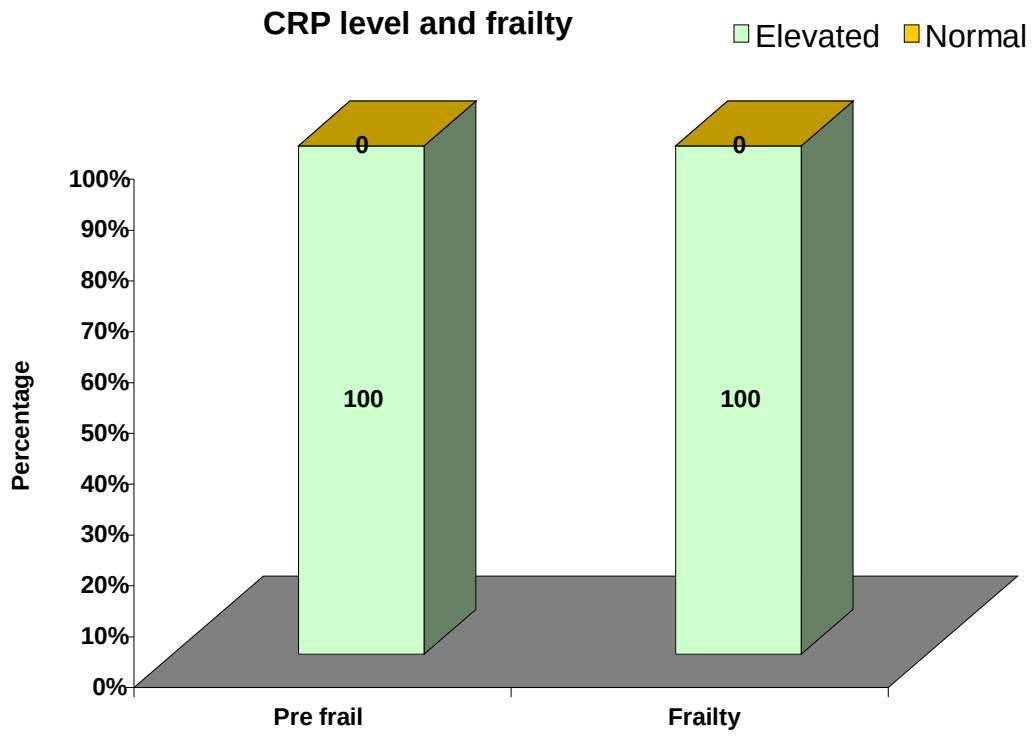


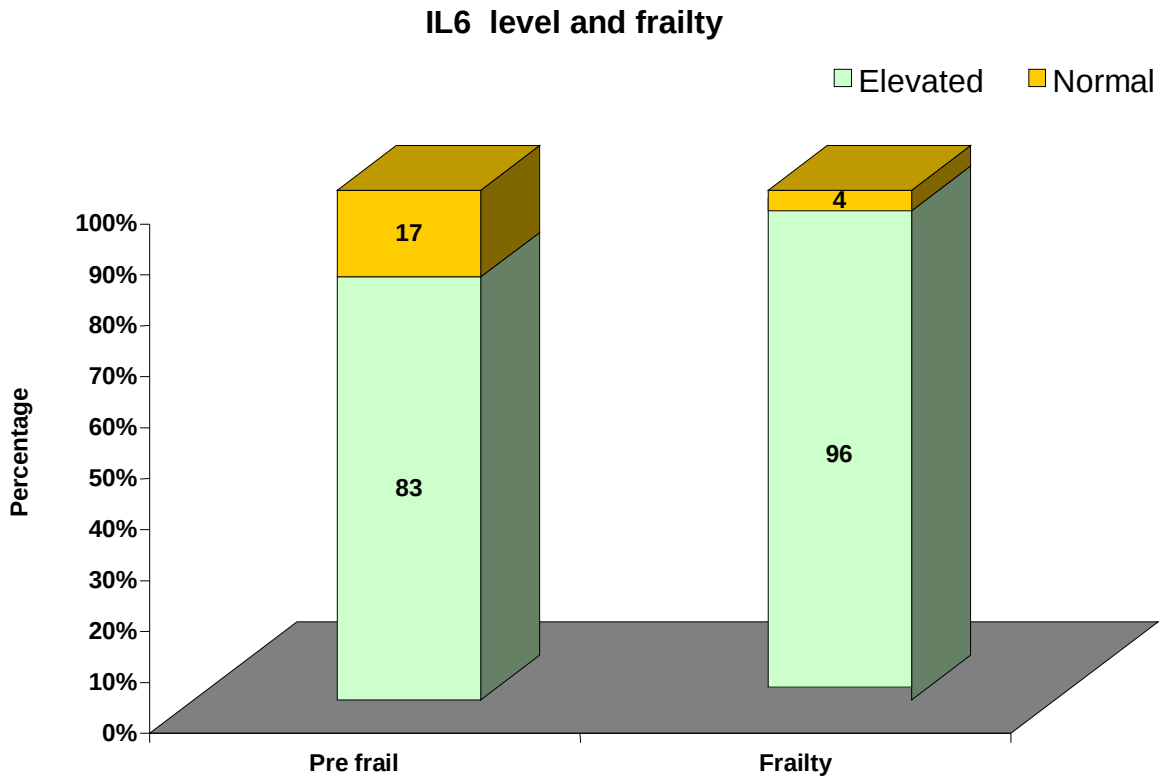

CRP level and Comorbid conditions
Elevated
Normal
Percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
100
Yes
No
DM
SHT
CAHD
CVA
Dementia

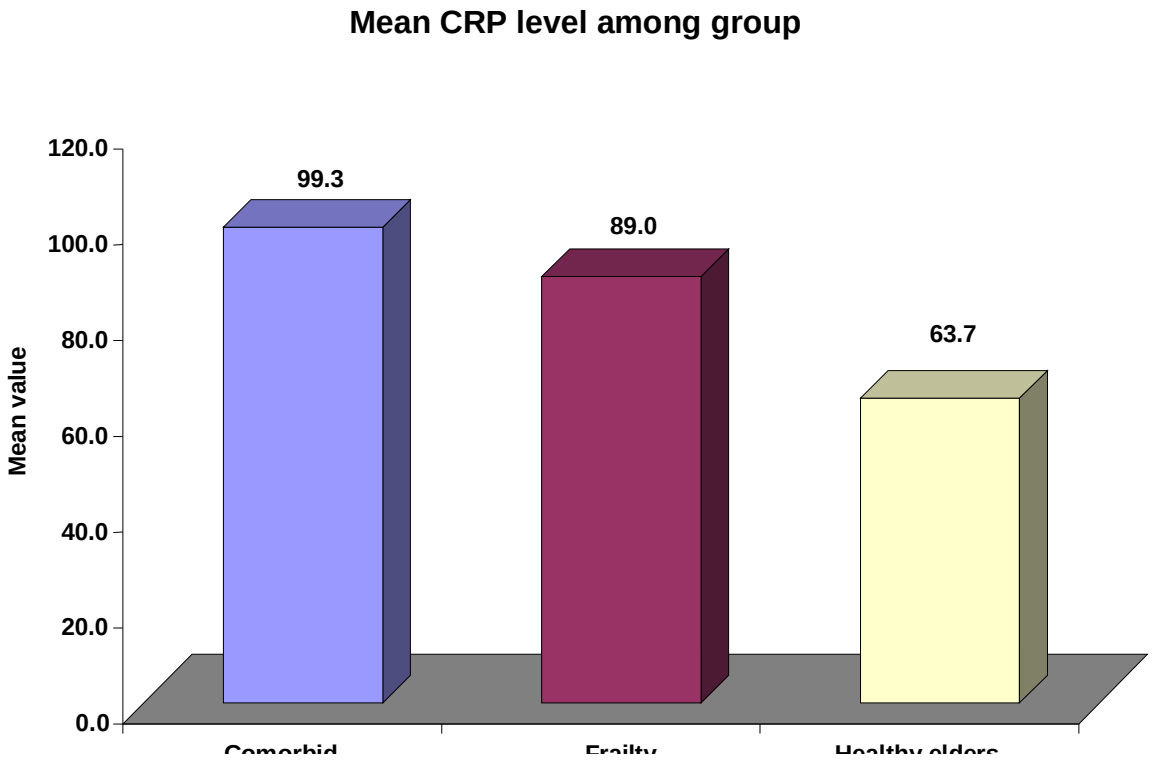

IL-6 level and Comorbid conditions
Elevated
Normal
Percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
100
19
81
10
90
10
90
0
100
14
86
33
67
4
96
20
80
8
92
Yes
No
DM
SHT
CAHD
CVA
Dementia

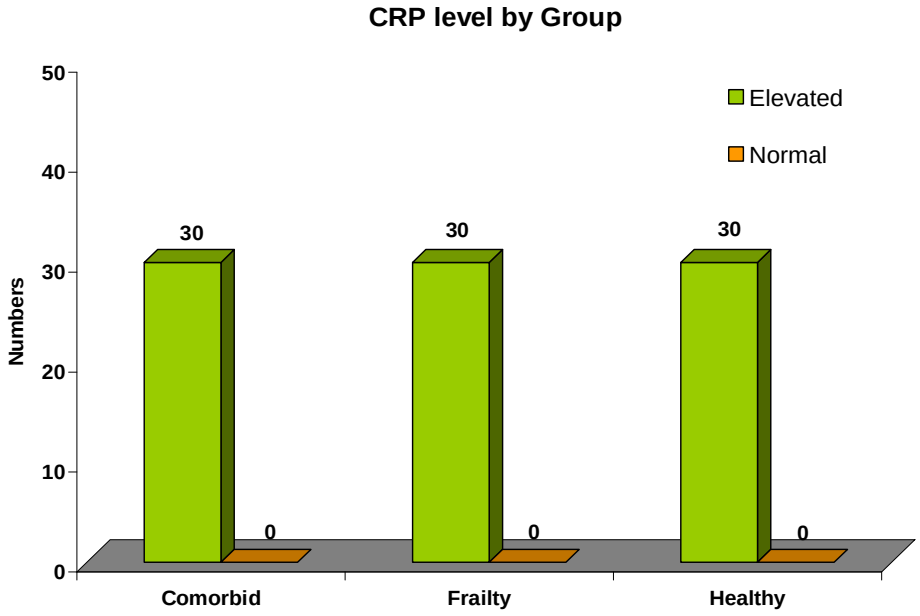
FRAILTY

	Frequency	Percent
Pre frail	6	20.0
Frailty	24	80.0
Total	30	100.0



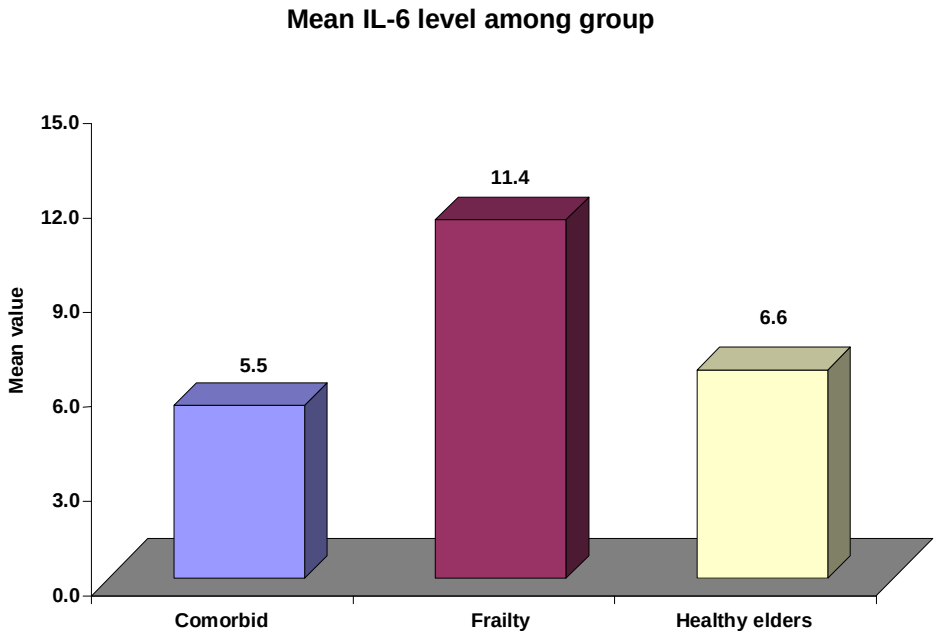

IL6 level and frailty
Elevated
Normal
Percentage
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
17
83
4
96
Pre frail
Frailty

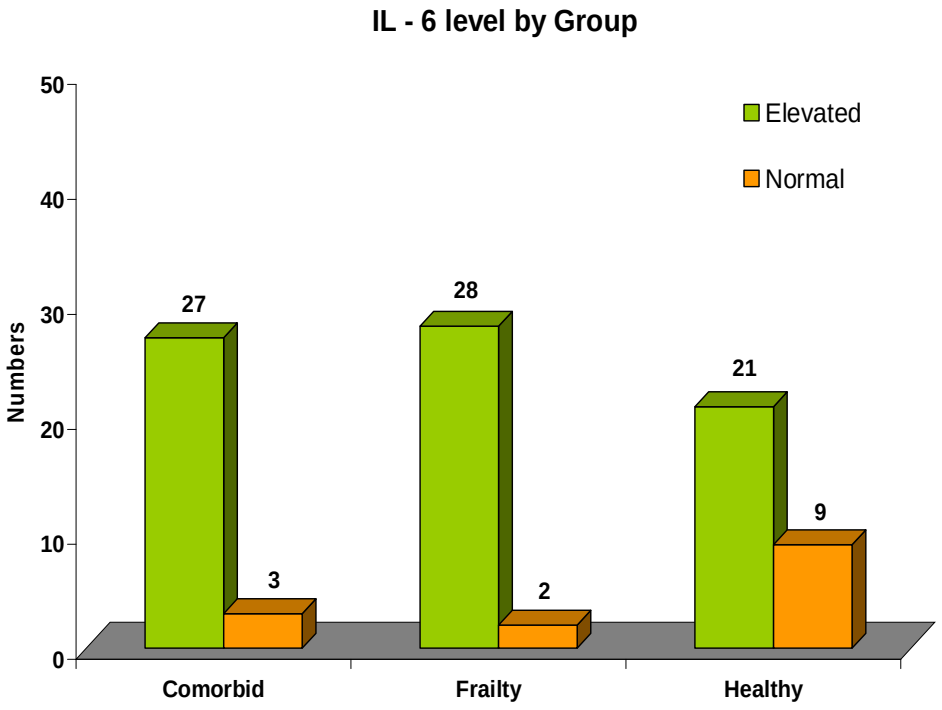

Mean CRP level among group
Mean value
120.0
100.0
80.0
60.0
40.0
20.0
0.0
99.3
89.0
63.7
Comorbid
Frailty
Healthy elders


CRP level by Group
Numbers
50
40
30
20
10
0
Elevated
Normal
30
30
30
0
0
0
Comorbid
Frailty
Healthy

CRP level Group

			Group			
			Comorbid	**Frailty**	**Healthy elders**	**Total**
CRP level	Elevated	Count	30	30	30	90
		% within Group	100.0%	100.0%	100.0%	100.0%
Total		Count	30	30	30	90
		% within Group	100.0%	100.0%	100.0%	100.0%

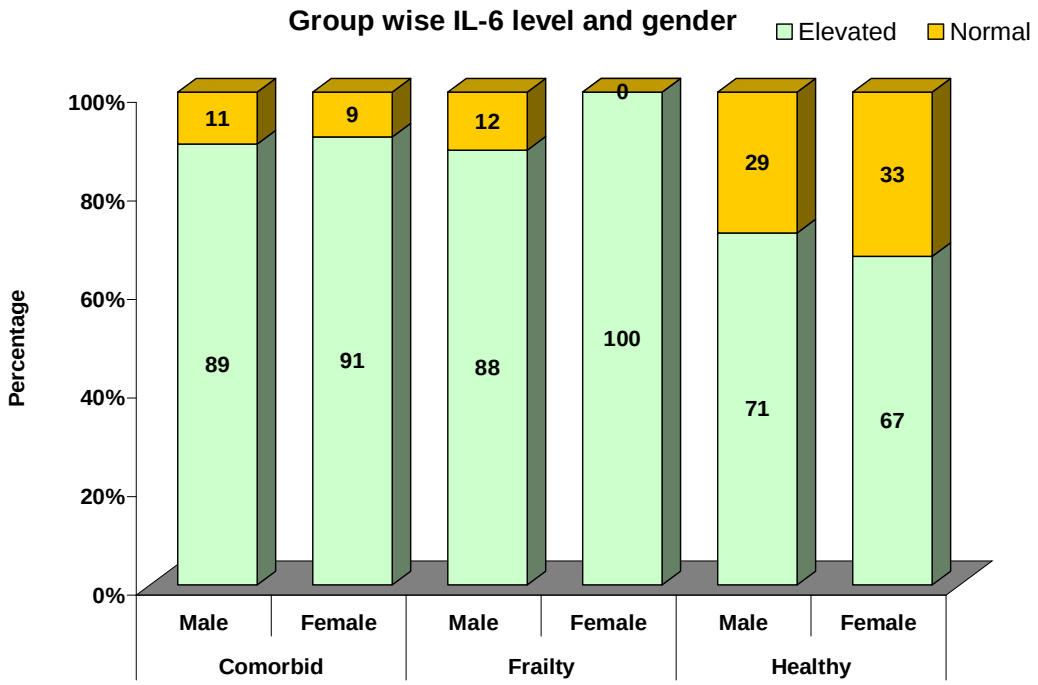

Mean IL-6 level among group
Mean value
15.0
12.0
9.0
6.0
3.0
0.0
5.5
11.4
6.6
Comorbid
Frailty
Healthy elders


IL - 6 level by Group
Numbers
50
40
30
20
10
0
Elevated
Normal
27
3
28
2
21
9
Comorbid
Frailty
Healthy

IL-6 level * Group

			Group			
			Comorbid	**Frailty**	**Healthy elders**	**Total**
IL-6 level	Normal	Count	3	2	9	14
		% within Group	10.0%	6.7%	30.0%	15.6%
	Elevated	Count	27	28	21	76
		% within Group	90.0%	93.3%	70.0%	84.4%
Total		Count	30	30	30	90
		% within Group	100.0%	100.0%	100.0%	100.0%

Chi-Square Value: 7.274 **P – Value: 0**.026 **Significant**



DISCUSSION

In this study inflammatory markers C-Reactive protein and Interleukin-6 of 90 elderly patients were analysed, under the three groups namely healthy elders, frail elders and elders with comorbid illness.

Among them 63% are males and 37% are females. In healthy elders 19 are male and 11 are female. In frailty group 17 are male and 13 are female. In elders with comorbid illness 21 are male and 9 are female.

The age distribution was 89% in age group of 75 to 80 years. 10% in age group of 81 to 90 years. Remaining 1% in age group of >90 years. More number of patients were found in age group of 75 to 80 years.

In the study group 28.9% were smokers and 71.1% were non smokers. C-Reactive protein levels are elevated in smokers as well as non smokers in all the three groups. Hence it is not a significant association. Where as Interleukin-6 levels are more elevated in smokers in healthy elders and elders with comorbid illness, than non smokers of the same groups.

In the comorbid group, diabetes was detected in 14, systemic hypertension in 20, Coronary heart disease in 8, stroke in 6 and dementia in 5 patients. CRP level are elevated in all the patients. Interleukin-6 level are elevated more in diabetic and coronary heart disease patients.

In the frailty group 6 were Pre frail and 24 were frail. CRP are elevated in both Pre frail and frail group. Interleukin-6 was elevated, more in frail group than in Pre frail group. 83% of patients in Pre frail group, and 96% of patients in frail group had elevated level of interleukin-6.

CRP levels are elevated in all the 3 groups. The mean CRP level was 63.7 in healthy elders, 89 in Frail elders, 99.3 in elders with comorbid illness. CRP is 10 fold increased in healthy elders, 15 fold increased in frail elders, 16.5 folds increased in elders with comorbid illness. Thus the patients with comorbid illness have higher CRP level.

In healthy elders 21(70%) have elevated level of interleukin-6. In frail elders 28(93%) have elevated level of interleukin-6. In comorbid illness 27 (90%)have elevated level of interleukin-6.

The mean interleukin-6 level was 6.6 in healthy elders, 11.4 in frail group, 5.5 in comorbid illness. Interleukin-6 is 3 fold increased in healthy elders, 6 fold in frail elders and 2.75 fold increased in elders with comorbid illness. Thus in frail elders interleukin-6 is more elevated.

In summary CRP level are elevated in all the three groups. In patients with comorbid illness CRP levels are higher compared with other two groups. Interleukin-6 level are elevated more in diabetes and coronary heart disease patients. Interleukin-6 is more elevated in frail elders.

CONCLUSION

1. CRP levels are elevated in all patients age more than 75 years.

2. Elders with comorbid illness have higher CRP level, compared to healthy groups.

3. Interleukin-6 levels are elevated in smokers, both in healthy group and in comorbid group.

4. Interleukin-6 level are elevated more in diabetic and coronary heart disease patients.

5. Interleukin-6 was elevated more in frail group than in Pre frail group.

BIBLIOGRAPHY

1. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol 2004;39(5):687-699.

2. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflammaging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–54.

3. Salvioli S, Capri M, Valensin S, Tieri P, Monti D, Ottaviani E, Franceschi C. Inflamm-Aging, Cytokines and Aging: State of the Art, New Hypotheses on the Role of Mitochondria and New Perspectives from Systems Biology. Current Pharmaceutical Design. 2006;12: 3161–3171.

4. De Martinis M, Franceschi C, Monti D, Ginaldi L. Inflamm-ageing and lifelong antigenic load as major determinants of ageing rate and longevity. FEBS Lett. 2005;11;579:2035–9.

5. Fagiola U, Cossarizza A, Scala E, Fanales-Belasio E, Ortolani C, Cozzi E, Monti D, Franceschi C, Paganelli R. Increased cytokine production in mononuclear cells of healthy elderly people. Eur J Immunol. 1993;23:2375–237.

6. Franceschi C, Monti D, Sansoni P, Cossarizza A. The immunology of exceptional individuals:the lesson of centenarians. Immunol Today. 1995;16:12–16.

7. Lio D, Scola L, Crivello A, Colonna-Romano G, Candore G, Bonafe M, Cavallone L, Marchegiani F, Olivieri F, Franceschi C, Caruso C. Inflammation, genetics, and longevity: further studies on the protective

effects in men of IL-10 -1082 promoter SNP and its interaction with TNF- -308 promoter SNP. J Med Genet. 2003;40:296–299.

8. Candore G, Colonna-Romano G, Balestrieri CR, Di Carlo D, Grimaldi MP, Listi F, Nuzzo D, Vasto S, Lio D, Caruso C. Biology of longevity: role of the innate immune system. Rejuvenation Res. 2006**;**9**:**143–148.

9. Vasto S, Candore G, Balestrieri CR, Caruso M, Colonna-Romano G, Grimaldi MP, Listi F, Nuzzo D, Lio D, Caruso C. Inflammatory networks in ageing, age-related diseases and longevity. Mech Aging Dev. 2006.

10. National institute of aging workshop on inflammation, inflammatory mediators, and aging, Bethesda, Maryland, September 1-2, 2004.

11. Hazzard's Geriatric medicine and Gerontology, 6th edition; part III, Vol.52; 2009.

12. Morley JE. Decreased food intake with aging. J Gerontol A Biol Sci Med Sci 2001;56 Spec No 2:81-88.

13. Morley JE. Anorexia, sarcopenia, and aging. Nutrition 2001;17(7-8):660-663.

14. Van der Mast RC. Pathophysiology of delirium. J Geriatr Psychiatry Neurol 1998;11(3):138-145, 157-158.

15. Kohut ML, Senchina DS. Reversing age-associated immunosenescence via exercise. Exerc Immunol Rev 2004;10:6-41.

16. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annu Rev Med 2000;51: 245-270.

17. Thomas DR. Anemia and quality of life: Unrecognized and undertreated. J Gerontol A Biol Sci Med Sci 2004;59:238-241.

18. Cesari M, Penninx BW, Lauretani F, et al. Hemoglobin levels and skeletal muscle: Results from the InCHIANTI study. J Gerontol A Biol Sci Med Sci 2004;59: 249-254.

19. Leng S, Chaves P, Koenig K, Walston J. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: A pilot study. J Am Geriatric Soc 2002;50;1268-1271.

20. Thomas DR. The relationship between functional status and inflammatory disease in older adults. J Gerontol A Biol Sci Med Sci 2003;58:995-998.

21. Reuben DB, Cheh AJ, Harris TB, et al. Peripheral blood markers of inflammation predict mortality and functional decline in high-functioning community-dwelling older persons. J Am Geriatric Soc 2002;50:638-644.

22. Cesari M, Pennix BW, Pahor M, et al. Inflammatory markers and physical performance in older persons: The Inchianti study. J Gerontol A Biol Sci Med Sci 2004;59:242-248.

23. Tilvis RS, Kahonen-Vare MH, Jolkkonen J, et al. Predictors of cognitive decline and mortality of aged people over a 10-year period. J Gerontol A Biol Sci Med Sci 2004;59:268-274.

24. Thompson D, Pepys MB, Wood SP. (1999). "The physiological structure of human C-reactive protein and its complex with phosphocholine.". Structure **7** (2): 169–77.

25. Pepys MB, Hirschfield GM (2003). "C-reactive protein: a critical update". J Clin Invest 111 (12): 1805.

26. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S (2005). "Adipokines: molecular links between obesity and atheroslcerosis". Am J Physiol Heart Circ Physiol 288 (5)

27. Tillett WS, Francis Jr T (1930). "Serological reactions in pneumonia with a nonprotein somatic fraction of pneumococcus" (PDF). J Exp Med 52: 561–585.

28. Clyne, Brian; Jonathan S. Olshaker (1999). "The C-reactive protein". Journal of Emergency Medicine 17 (6): 1019–1025

29. Lloyd-Jones DM, Liu K, Tian L, Greenland P (5 June 2006). "Narrative review: assessment of C-reactive protein in risk prediction for cardiovascular disease". Ann Intern Med 145 (1): 35–42.

30. American Heart Association. Inflammation, Heart Disease and Stroke.

31. Pradhan AD; Manson, JE; Rifai, N; Buring, JE; Ridker, PM (2001). "C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus". JAMA 286 (3): 327–334.

32. Dehghan A; Kardys, I; De Maat, MP; Uitterlinden, AG; Sijbrands, EJ; Bootsma, AH; Stijnen, T; Hofman, A et al. (2007). "Genetic variation, C-reactive protein levels, and incidence of diabetes". Diabetes 56 (3): 872.

33. Ridker PM, Danielson E, et al. (November 2008). "Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein". N. Engl. J. Med. 359 (21): 2195–207.

34. Ferguson-Smith AC, Chen YF, Newman MS, May LT, Sehgal PB, Ruddle FH (April 1988). "Regional localization of the interferon-beta 2/B-cell stimulatory factor 2/hepatocyte stimulating factor gene to human chromosome 7p15-p21". Genomics 2 (3): 203–8.

35. Van der Poll T, Keogh CV, Guirao X, Buurman WA, Kopf M, Lowry SF (1997). "Interleukin-6 gene-deficient mice show impaired defense against pneumococcal pneumonia". J Infect Dis 176 (2): 439–44

36. Febbraio MA, Pedersen BK (2005). "Contraction-induced myokine production and release: is skeletal muscle an endocrine organ?". Exerc Sport Sci Rev 33 (3): 114–9.

37. J Am Geriatr Soc. 1993 Feb;41(2):176-81.,Ershler WB.Geriatrics Research, and Clinical Center (GRECC), Madison, WI.

38. The Institute for the Advanced Studies in Aging and Geriatric Medicine, Washington DC, 20006; Ann Arbor, Michigan, 48109; 1.Inflammatory mediators in the elderly Karen.

39. Age-Associated Increased Interleukin-6 Gene Expression, Late-Life Diseases, and Frailty, Annual Review of Medicine, Vol. 51: 245-27, William B. Ershler and Evan T. Keller.

40. Ferrucci L, Harris TB, Guralnik JM, Tracy RP, Corti MC, Cohen HJ, Penninx B, Pahor M, Wallace R, Havlik RJ Geriatric Department, I Fraticini, National Research Institute (INRCA), Florence, Italy. J Am Geriatr Soc. 1999 Jun;47(6):755-6.

41. Barton BE August 2005. "Interleukin-6 and new strategies for the treatment of cancer, hyperproliferative diseases and paraneoplastic syndromes". Expert Opin. Ther. Targets 9 (4): 737–52.

42. Smolen JS, Maini RN 2006. "Interleukin-6: a new therapeutic target". Arthritis Res. Ther. 8 Suppl 2: S5

43. Sean X. Leng and Linda P. FriedInflammatory Markers and Frailty, Hand book on immunosenecence, part 17: 20091.

44. Hazzard's Geriatric medicine and Gerontology, 6th edition; part III, Vol.52; 2009.

45. Luigi Ferrucci, National institute of aging workshop on inflammation, inflammatory mediators, and aging, Bethesda, Maryland, September 1-2, 2004.

46. Morley JE. Anorexia, sarcopenia, and aging. Nutrition 2001;17:660–3.

47. Morley JE, Baumgartner RN, Roubenoff R, et al. Sarcopenia. J Lab Clin Med 2001;137:

48. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889–96.

49. Forrest KY, Zmuda JM, Cauley JA. Patterns and determinants of muscle strength change with aging in older men. Aging Male 2005;8:151–6.

50. Fried LP, Tangen CM, Walston J, et al. Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol Med Sci 2001;56A:M146–56.

51. Age and aging. The journal of the british geriatric society, volume 39, no 3, may 2010.

52. John E. Morley, M.D. Frailty: Management and Treatment, June 1, 2002

53. Sattar N, Murray HM, Welsh P, Blauw GJ, Buckley BM, et al. (2009) Are Markers of Inflammation More Strongly Associated with Risk for Fatal Than for Nonfatal Vascular Events? PLoS Med 6(6): e1000099,

54. Dallas**,** The researchers, headed by Dr Matteo Cesari (Wake Forrest University School of Medicine, Winston-Salem, NC), 20 OCT 2003 20:00:00 | Julia Rommelfanger

55. Diabetes Technology & Therapeutics Volume 8, Number 1, 2006 Mary Ann Liebert**,** Mary M. Kimberly, Ph.D., Gerald R. Cooper, M.D., Ph.D.,And Gary L. Myers,

56. Schmidt MI, Duncan BB, Sharrett AR, Lindberg G, Savage PJ, Offenbacher S, Azambuja MI, Tracy RP, Heiss G: Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities Study): a cohort study. Lancet353 :1649 –1652,1999.

57. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA286 :327 –334,2001.

58. Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, Tracy RP: The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. Diabetes50 :2384 –2389,2001.

59. Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean ME, Haffner SM: Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. Diabetes Care25 :2016 –2021,2002.

60. Indsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, Knowler WC, Krakoff J: Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet360 : 57 –58,2002.

61. Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA: High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes51 :455 –461,2002.

62. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, O'Reilly DS, Packard CJ, Sattar N: C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes51 :1596 –1600,2002.

63. Ford ES: Leukocyte count, erythrocyte sedimentation rate, and diabetes incidence in a national sample of US adults. Am J Epidemiol155 :57 –64,2002.

64. Nakanishi N, Yoshida H, Matsuo Y, Suzuki K, Tatara K: White blood-cell count and the risk of impaired fasting glucose or type II diabetes in middle-aged Japanese men. Diabetologia45 :42 –48,2002.

65. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM: Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. Diabetes51 :1131 –1137,2002.

66. Saito M, Ishimitsu T, Minami J, Ono H, Ohrui M, Matsuoka H. Relations of plasma high-sensitivity C-reactive protein to traditional cardiovascular risk factors. Atherosclerosis 2003; 167: 73-9.

67. Ramadori G, Christ B**:** Cytokines and the hepatic acute-phase response**.** Semin Liver Dis 1999 , 19**:**141-155.

68. Muir KW, Weir CJ, Alwan W, Squire IB, Lees KR: C-reactive protein and outcome after ischemic stroke. Stroke 1999 , 30:981-985.

69. De Luigi A, Fragiacomo C, Lucca U, Quadri P, Tettamanti M, Grazia De Simoni M.Department of Neuroscience, Mario Negri Insitute for Pharmacological Research, Via Eritrea, 62, 20157, Milano, Italy.

70. Giovanni Ravagliaa, Paola Fortia, Fabiola Maiolia, Martina Chiappellib, Fausta Montesia, Emanuela Tuminib, Erminia Marianic, Federico Licastrob, Christopher Pattersond Received 20 March 2006; received in revised form 26 July 2006; accepted 31 August 2006. published online 04 October 2006.

PROFORMA

Name

Age

Sex

IP/OP No

C/O

Co/morbid illness

	History	Duration	Treatment
DM			
SHT			
CAHD			
CVA			
Dementia			

Personal H/O:
Smoker
Alcoholic

General Examination
BP
PR
Systemic Examination

Mini mental score

Score

FRIED'S crieteria for frailty:

1.Gait speed :

2.Hand grip strength :

3.Weight loss :

4.Physical activity :

5.Self reported physical exhaustion :

Score:

Investigation:

ESR	**Hemoglobin**	**Blood sugar**	**Urea**	**Creatinine**	**Lipid profile**

ECG	
CXR-PA	
CT Brain	

IL-6	
CRP	

Impression: 1.Healthy elder 2.Frail elder 3.Elders with comorbid illness.

ELDERLY WITH COMORBID ILLNESS

No	Age	Sex	DM	SHT	CHD	CVA	Deme ntia	Duration	Smo-king	Alcohol
1	75	M	No	Yes	No	No	No	10yrs	No	No
2	88	M	No	Yes	No	No	No	3yrs	No	No
3	77	M	Yes	Yes	No	No	No	DM 1&1/2yrs, SHT 8yrs	Quit 30yrs	Yes
4	82	M	No	No	No	Yes	No	2yrs	Quit 10Yrs	Quit 10 Yrs
5	79	M	Yes	No	Yes	No	No	20yrs	Quit 15yrs	Yes
6	80	M	Yes	Yes	No	No	No	DM 2months SHT 10yrs	No	No
7	77	M	No	Yes	No	No	No	3yrs	No	No
8	76	M	No		Yes	No	No	10yrs	No	No
9	75	F	Yes	Yes	No	No	No	DM 15yrs SHT 4months	No	No
10	80	M	No	Yes	Yes	No	No	20yrs	No	Yes
11	75	M	No	No	No	Yes	No	1 week	No	No
12	80	M	No	Yes	No	No	No	5yrs	Quit 15yrs	Quit 3Yrs
13	75	M	Yes	Yes	No	Yes	No	10yrs	No	Yes
14	80	M	Yes	Yes	No	No	No	20yrs	No	No
15	80	M	No	Yes	Yes	No	No	10yrs	Quit 25yrs	Quit 25Yrs
16	78	F	Yes	Yes	Yes	No	No	10yrs	No	No
17	78	F	No	Yes	No	No	No	20yrs	No	No
18	75	F	No		Yes	No	No	2yrs	No	No
19	75	F	Yes	Yes	No	No	No	DM 6months SHT 4yrs	No	No

No	Age	Sex	DM	SHT	CHD	CVA	Dementia	Duration	Smo-king	Alcohol
20	75	F	Yes	Yes	No	No	No	2yrs	No	No
21	75	F	Yes	Yes	No	No	No	5yrs	No	No
22	80	M	No	Yes	No	No	No	10yrs	No	No
23	78	F	No	Yes	No	No	No	10yrs	No	No
24	75	F	Yes	Yes	No	No	No	10yrs	No	No
25	75	M	Yes	Yes	Yes	No	No	20yrs	Quit 20Yrs	Quit 20Yrs
26	75	F	No	No	No	Yes	No	1yrs	No	No
27	78	M	No	Yes	No	Yes	Yes	10yrs	No	No
28	75	M	Yes	No	No	No	No	25yrs	Yes	Yes
29	75	M	No	No	Yes	No	No	3yrs	Yes	No
30	75	F	No	No	No	Yes	No	10yrs	No	No

FRAIL ELDERS

No	Age	Sex	DM	SHT	CHD	CVA	Dementia	Duration	smoking	Alcohol
31	96	M	No	No	No	No	No	No	No	No
32	80	F	No	No	No	No	No	No	No	No
33	75	F	No	No	No	No	No	No	No	No
34	76	M	No	No	No	No	No	No	Quit 5Yrs	No
35	89	M	No	No	No	No	No	No	No	No
36	75	M	No	No	No	No	No	No	No	No
37	80	F	No	No	No	No	No	No	No	No
38	80	M	No	No	No	No	No	No	No	No
39	76	M	No	No	No	No	No	No	Quit 20Yrs	No
40	88	F	No	No	No	No	No	No	No	No
41	81	M	No	No	No	No	No	No	Yes	No
42	76	M	No	No	No	No	No	No	Quit 30Yrs	Quit 40Yrs
43	75	F	No	No	No	No	No	No	No	No
44	83	M	No	No	No	No	No	No	Yes	No
45	80	M	No	No	No	No	No	No	Yes	Quit 2Yrs
46	75	M	No	No	No	No	No	No	No	No
47	90	M	No	No	No	No	No	No	Yes	No
48	75	M	No	No	No	No	No	No	No	No
49	75	M	No	No	No	No	No	No	No	No
50	81	M	No	No	No	No	No	No	No	No
51	76	M	No	No	No	No	No	No	No	Quit 10Yrs
52	80	F	No	No	No	No	No	No	No	No
53	75	F	No	No	No	No	No	No	No	No
54	80	F	No	No	No	No	No	No	No	No
55	75	F	No	No	No	No	No	No	No	No
56	75	F	No	No	No	No	No	No	No	No
57	80	F	No	No	No	No	No	No	No	No
58	75	F	No	No	No	No	No	No	No	No
59	75	F	No	No	No	No	No	No	No	No
60	75	M	No	No	No	No	No	No	Quit 1Yr	Quit 1Yr

HEALTHY ELDERS

No	Age	Sex	DM	SHT	CHD	CVA	DEMENTIA	Duration	Smoking	Alcohol
61	80	M	No	No	No	No	No	No	No	No
62	75	M	No	No	No	No	No	No	No	No
63	75	M	No	No	No	No	No	No	No	No
64	75	F	No	No	No	No	No	No	No	No
65	76	F	No	No	No	No	No	No	No	No
66	80	F	No	No	No	No	No	No	No	No
67	75	F	No	No	No	No	No	No	No	No
68	79	F	No	No	No	No	No	No	No	No
69	76	F	No	No	No	No	No	No	No	No
70	76	F	No	No	No	No	No	No	No	No
71	75	M	No	No	No	No	No	No	No	No
72	75	M	No	No	No	No	No	No	No	No
73	75	M	No	No	No	No	No	No	No	No
74	75	M	No	No	No	No	No	No	Quit 5Yrs	No
75	76	M	No	No	No	No	No	No	Quit 10Yrs	No
76	80	M	No	No	No	No	No	No	Quit 20Yrs	Quit 20Yrs
77	75	M	No	No	No	No	No	No	No	No
78	75	F	No	No	No	No	No	No	No	No
79	75	M	No	No	No	No	No	No	Quit 10Yrs	No
80	75	M	No	No	No	No	No	No	Quit 5Yrs	Quit 5Yrs
81	75	M	No	No	No	No	No	No	Quit 5Yrs	Quit 5Yrs
82	78	F	No	No	No	No	No	No	Quit 1yr	No
83	75	M	No	No	No	No	No	No	No	No
84	83	M	No	No	No	No	No	No	Quit 15Yrs	No
85	84	M	No	No	No	No	No	No	Quit 40Yrs	No
86	80	M	No	No	No	No	No	No	No	No
87	80	M	No	No	No	No	No	No	Quit 2Yrs	Quit 2Yrs
88	75	M	No	No	No	No	No	No	Quit 10Yrs	Quit 10Yrs
89	75	M	No	No	No	No	No	No	No	No
90	80	M	No	No	No	No	No	No	No	No

ELDERLY WITH COMORBID ILLNESS

No	MMSE	Education	Frailty Score	Hb	ESR	Blood Sugar	Urea	Creatinine	Total Chosterol	TGL	HDL
1	27/30	7th std	0/5	12.6	22	122	26	.9	148	72	38
2	27/30	8th std	0/5	11.2	38	136	24	1	162	82	51
3	29/30	9th std	0/5	11.5	50	75	40	.9	171	105	42
4	9/30	6th std	3/5	11.6	16	94	32	1	160	110	45
5	28/30	9th std	0/5	11.7	22	233	43	1.4	152	121	36
6	29/30	8th std	2/5	11.6	18	185	21	.7	162	113	40
7	29/30	6th std	0/5	8	47	86	49	1	198	84	50
8	30/30	SSLC	0/5	11.8	52	78	22	.9	200	82	30
9	28/30	5th std	4/5	11.2	17	252	30	.9	161	95	43
10	30/30	6th std	0/5	10	15	86	24	.9	205	136	36
11	27/30	8th std	2/5	9.9	30	94	30	2.2	206	110	39
12	28/30	6th std	0/5	13.7	25	103	30	1.0	259	193	56
13	21/30	illiterate	2-5	11.9	45	93	25	.9	149	136	34
14	28/30	BSc	0/5	12.5	10	114	24	.9	154	88	39
15	29/30	SSLC	1/5	11.7	45	118	32	1.3	145	119	35
16	25/30	5th std	2/5	10	22	204	22	.9	236	278	55
17	28/30	illiterate	0/5	11.7	25	139	29	.8	208	128	48
18	22/30	8th std	3/5	10.6	32	110	19	.9	170	136	52
19	30/30	8th std	4/5	9	39	122	26	1	165	105	36
20	27/30	6th std	2/5	8.8	42	134	28	1.1	178	151	46
21	27/30	3rd std	0/5	12.8	28	142	32	1.4	226	132	40
22	27/30	SSLC	0/5	12	21	132	30	1.1	158	129	42
23	30/30	SSLC	0/5	9.1	32	106	32	1.0	192	126	38
24	30/30	SSLC	1/5	8.8	36	162	34	1.1	158	148	42
25	25/30	6th std	2/5	8.6	18	191	19	1	152	100	35
26	26/30	6th std	2/5	11.1	28	106	18	.9	212	136	48
27	16/30	Advocate	3/5	11.6	29	116	22	1.1	188	162	52
28	27/30	SSLC	2/5	12.8	21	136	32	1.3	182	161	39
29	30/30	SSLC	0/5	13.1	18	111	31	1.2	161	138	28
30	3/30	SSLC	0/5	12.8	18	109	34	1.4	156	142	40

FRAIL ELDERS

No	MMSE	Edu-cation	Frailty Score	Hb	ESR	Blood Sugar	Urea	Creatinine	Total cholesterol	TGL	HDL
31	18/30	4th std	5/5	10	20	72	46	1.3	192	121	37
32	27/30	illiterate	3/5	10.8	18	101	28	.9	169	132	36
33	26/30	illiterate	5/5	11	21	108	28	1.1	162	156	39
34	30/30	SSLC	3/5	10.4	29	95	28	1	179	261	40
35	28/30	SSLC	3/5	11	29	74	25	.9	143	71	35
36	28/30	8th std	4/5	13.1	86	90	36	1.1	158	80	45
37	24/30	7th std	5/5	10.2	7	88	28	.9	270	120	36
38	28/30	8th std	3/5	12	25	98	28	.7	175	268	45
39	29/30	9th std	4/5	7.6	65	126	37	1.4	142	74	36
40	26/30	illiterate	5/5	11	16	128	26	.8	281	150	36
41	28/30	8th std	4/5	11.1	84	79	45	1.5	149	120	34
42	28/30	8th std	1/5	9	8	82	35	1	124	181	38
43	30/30	SSLC	2/5	9.6	22	121	19	.9	156	131	38
44	27/30	SSLC	5/5	10.4	66	89	27	1	167	80	36
45	28/30	5th std	5/5	11.8	30	93	26	1	152	144	30
46	25/30	6th std	1/5	9.6	9	96	41	1.1	146	72	42
47	14/30	illiterate	5/5	10.1	15	106	45	1.4	210	110	38
48	18/30	7th std	4/5	13.7	105	81	21	1.8	178	132	36
49	26/30	7th std	5/5	6.2	88	96	38	1.1	142	137	38
50	25/30	7th std	4/5	10.6	136	111	39	1.2	153	84	46
51	30/30	8th std	3/5	11.1	16	112	28	1	206	179	42
52	27/30	6th std	3/5	8.9	28	121	28	.9	205	126	48
53	30/30	8th std	3/5	12	32	82	28	.9	161	96	36
54	29/30	SSLC	3/5	12.6	32	72	30	1	162	136	38
55	29/30	7th std	3/5	11.6	31	116	28	1.4	161	146	39
56	26/30	illiterate	4/5	8.9	32	142	28	1.1	156	148	40
57	22/30	illiterate	5/5	8.4	54	92	26	1	196	120	39
58	27/30	6th std	2/5	12.6	32	126	29	.9	156	144	40
59	29/30	7th std	2/5	8.9	18	132	29	.9	151	148	40
60	23/30	illiterate	2/5	9.3	10	117	22	1	145	167	37

HEALTHY ELDERS

No	MMSE	Edu-cation	Frailty Score	Hb	ESR	Blood Sugar	Urea	Creati nine	Total Chol-esterol	TGL	HDL
61	30/30	BE	0/5	11.9	13	90	38	1.1	189	116	36
62	30/30	SSLC	0/5	9.8	18	121	32	1.2	169	136	36
63	27/30	4th std	0/5	10.6	13	89	28	1.2	189	126	38
64	27/30	6th std	0/5	8.9	29	189	32	1.1	144	72	36
65	29/30	4th std	0/5	10.1	26	106	29	.9	146	126	36
66	30/30	7th std	0/5	9.2	22	89	32	1.1	142	221	42
67	26/30	illiterate	0/5	9.8	31	136	31	1.4	156	144	36
68	29/30	7th std	0/5	8.9	42	156	29	1.1	210	72	36
69	30/30	5th std	0/5	10.6	86	116	29	1.1	149	119	35
70	29/30	8th std	0/5	12	26	126	32	1.1	138	108	34
71	28/30	7th std	0/5	13	26	106	28	.9	158	132	38
72	28/30	5th std	0/5	11	42	98	32	.9	178	140	38
73	30/30	SSLC	0/5	8.8	23	103	30	1	176	128	38
74	29/30	8th std	0/5	9.2	32	106	32	.9	192	136	32
75	27/30	6th std	0/5	11.9	28	89	32	1.1	189	136	31
76	29/30	8th std	0/5	12.3	52	89	33	1.2	212	136	30
77	28/30	9th std	0/5	11	10	118	23	.9	162	136	36
78	27/30	6th std	0/5	8.9	22	106	33	1.3	152	146	38
79	27/30	6th std	0/5	9.2	32	134	32	.7	132	162	34
80	24/30	illiterate	0/5	8.3	46	134	42	1.4	112	156	56
81	26/30	illiterate	0/5	9.8	34	109	31	1.1	142	192	48
82	29/30	illiterate	0/5	10.2	15	83	18	.7	232	201	48
83	30/30	9th std	0/5	13	11	88	25	.9	226	75	30
84	30/30	8th std	0/5	9	60	72	30	.9	193	87	33
85	27/30	8th std	0/5	7.9	48	99	29	.9	172	131	39
86	29/30	6th std	0/5	11	45	81	20	.6	210	106	52
87	28/30	1st std	0/5	11.6	17	135	21	.7	131	158	38
88	30/30	6th std	0/5	10.5	11	86	24	.8	199	182	33
89	28/30	Teacher	0/5	11	75	68	27	.9	161	136	38
90	29/30	8th std	0/5	12.1	21	106			148	151	40

ELDERLY WITH COMORBID ILLNESS

No	ECG	CXP-PA	CT Brain	CRP	IL-6
1	NSR, WNL	Normal	Right MCA infarct	120	6
2	NSR, incomplete RBBB	Aortic knuckle prominent	--	90	4
3	NSR, WNL	Unfolding of Aorta, Cardiomegaly	--	90	6
4	AF, CVR	Cardiomegaly	Bilateral MCA infarct	150	4
5	Sinus tachycardia, old IWMI	Increased bronchovascular marking	--	90	3
6	NSR, LVH	Bilateral hilar opacity	--	190	5
7	NSR, LVH	LV Configuration	--	90	3
8	Poor recording	Bilateral hilar opacity	--	90	4
9	NSR, WNL	Cardiomegaly, LV Configuration	--	190	10
10	NSR, incomplete RBBB	Normal	--	190	10
11	NSR, WNL	Normal	Right MCA infarct	50	1
12	NSR, WNL	Rt Costo phrenic angle obliteration	--	50	4
13	NSR, LVH	Aortic knuckle prominent	Left MCA infarct	70	6
14	NSR, WNL	Right hilar Opacity	--	80	3
15	NSR, WNL	Normal	--	190	10
16	2^{nd} degree AV block, mobitz type II	Cardiomegaly	--	90	3
17	LBBB	Increased bronchovascular marking, Aortic knuckle prominent	--	70	1
18	NSR, WNL	Normal	--	90	6
19	NSR, WNL	Cardiomegaly	--	90	4
20	NSR, WNL	Normal	--	80	6

ELDERLY WITH COMORBID ILLNESS

No	ECG	CXR-PA	CT Brain	CRP	IL-6
21	NSR, WNL	LV Configuration	--	90	6
22	NSR, WNL	Normal	--	60	8
23	NSR, LAD	Normal	--	190	6
24	NSR, LVH Strain	LV Configuration	--	80	6
25	NSR, PPRW	Normal	--	50	6
26	NSR, WNL	Normal	Right MCA infarct	90	5
27	NSR, LVH	Cardiomegaly	Multi infarct	80	2
28	NSR, WNL	Normal	--	50	6
29	Old IWMI	Normal	--	50	15
30	NSR, WNL	Normal	Multi infarct	90	6

FRAIL ELDERS

No	ECG	CXR-PA	CT Brain	CRP	IL-6
31	NSR, WNL	Normal	--	90	4
32	NSR, WNL	Unfolding of Aorta	--	190	4
33	NSR, WNL	Normal	--	80	8
34	NSR, LAD,LVH	Bilateral hilar Opacity	--	50	6
35	NSR, WNL	Aortic knuckle prominent	--	50	4
36	NSR, WNL	Increased broncho Vascular marking	--	80	5
37	NSR, WNL	Unfolding of Aorta	--	90	25
38	LAD, RBBB	Normal	--	90	6
39	NSR, LAD, old IWMI	Cardiomegaly	--	90	10
40	NSR, WNL	Normal	--	90	10
41	NSR, WNL	Normal	--	50	5
42	NSR, WNL	Normal	--	70	2
43	NSR, WNL	LVH configuration	--	190	30
44	NSR, WNL	Tubular heart, emphysematous chest	--	90	2
45	NSR, WNL	Normal	--	70	25
46	NSR, WNL	Normal	--	50	3
47	NSR, WNL	Normal	--	30	10
48	NSR, WNL	Normal	--	50	15
49	ST	Normal	--	190	10
50	NSR, WNL	Normal	--	90	5
51	NSR,WNL	Normal	--	70	5
52	NSR,WNL	Normal	--	190	20
53	NSR,WNL	Normal	--	90	20
54	NSR,T wave Inversion in V1,V2	Normal	--	80	20
55	NSR,LAD, old IWMI	Normal	--	60	25
56	NSR, incomplete RBBB	Unfolding of aorta	--	90	10
57	NSR, PPRW	Increased Broncho vascular marking	--	90	15
58	Sinus Arrhythmia	Normal	--	110	4
59	NSR, LVH	LVH configuration	--	60	4
60	NSR, WNL	Left hilar opacity	--	50	30

HEALTHY ELDERS

No	ECG	CXR-PA	CT Brain	CRP	IL-6
61	NSR, WNL	Increased bronchovascular marking	--	50	15
62	NSR, PPRW	Rt hilar opacity present	--	30	20
63	NSR, Incomplete RBBB	Normal	--	50	4
64	Sinus arrhythmia	Increased bronchovascular marking	--	90	2
65	NSR, WNL	Normal	--	80	4
66	NSR, WNL	Aortic knuckle prominent	--	110	2
67	NSR, WNL	Normal	--	30	2
68	NSR, PPRW	Normal	--	90	3
69	NSR, WNL	Increased bronchovascular marking	--	50	4
70	NSR, WNL	Normal	--	60	4
71	NSR, WNL	Normal	--	90	2
72	NSR, WNL	Aortic knuckle prominent	--	40	2
73	NSR, WNL	Normal	--	60	20
74	NSR, PPRW	Normal	--	80	8
75	NSR, WNL	Normal	--	90	8
76	NSR, WNL	Increased bronchovascular marking	--	90	2
77	NSR, WNL	Normal	--	40	5
78	NSR, WNL	Increased bronchovascular marking	--	90	10
79	NSR, WNL	Normal	--	30	10
80	NSR, WNL	Normal	--	50	5
81	Incomplete RBBB	Normal	--	40	5
82	NSR, PPRW	Normal	--	90	25
83	NSR, WNL	Unfolding of aorta	--	70	2
84	Occasional atrial Ectopics present	Increased bronchovascular marking	--	40	4
85	NSR, WNL	Normal	--	70	4
86	NSR, WNL	Normal	--	90	1
87	NSR, WNL	Normal	--	50	2
88	NSR, WNL	Normal	--	40	10
89	NSR, WNL	Normal	--	70	10
90	NSR, WNL	Normal	--	50	4

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. S. Sabitha
Pg in MD Geriatric
Madras Medical College, Chennai -3
Dear S. Sabitha

The Institutional Ethical Committee of Madras Medical College reviewed and discussed your application for approval of the project / proposal / clinical trail entitled " **Inflammatory markers level in elderly with co-morbid illness, without co-morbid illness and frail elders**" No 11092010.

The following members of Ethical committee were present in the meeting held on 14.09.2010 conducted at Madras Medical College, Chennai -3.

1. Prof. S.K. Rajan, MD -- Chairperson
2. Prof. J. Mohanasundaram, MD,Ph.D,DNB -- Deputy Chairman
   Dean, Madras Medical College, Chennai -3
3. Prof. A. Sundaram, MD -- Member Secretary
   Vice Principal , MMC, Chennai -3
4. Prof. R. Sathianathan, MD -- Member
   Director, Institute of Psychiatry
5. Prof R. Nandhini, MD -- Member
   Director, Institute of Pharmacology, MMC, Ch-3
6. Prof. C. Rajendran , MD -- Member
   Director, Institute of Internal Medicine, MMC, Ch-3
7. Prof. Geetha Subramanian, MD,DM -- Member
   Professor & Head , Dept. Of Cardiology
8. Prof. V. Shruti Kamal, MS -- Member
   Professor of Surgery, MMC, Ch-3
9. Prof. Md. Ali, MD, DM -- Member
   Professor & Head ,,Dept. of MGE, MMC, Ch-3
10. Tmt.Arnold Saulina, -- Member
    Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee